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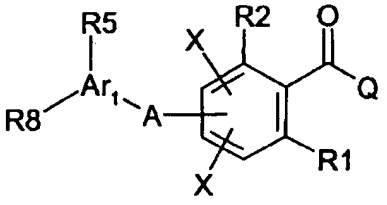
(54) Title: NOVEL METHOXYBENZAMIDE COMPOUNDS FOR USE IN MCH RECEPTOR RELATED DISORDERS



(I)

(57) Abstract: Novel compounds of Formula (I) which modulate MCH activity are disclosed, in which A is a linker; Ar_1 is an aryl or heteroaryl group; R1 is a lower alkoxy group; R2 is an R1 group or hydrogen, an OH or an NH_2 group, Q together with the carbonyl forms an amide group, which is further substituted with an amine group; R5 is selected from hydrogen, halogen atoms, alkoxy groups, hydroxy, alkylamino groups, dialkylamino groups, hydroxylalkyl groups, carboxamido groups, acylamido groups, acyl groups, -CHO, nitrile, alkyl, alkenyl or alkynyl groups, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2NAlk_2$, $-SO_2Alk$; X is H, F, Cl, Br, I, $-SCH_3$, $-CF_3$, $-OCF_3$, $-SCF_3$, OCH_3, or lower alkyl or alkenyl group; R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups, aryl groups, heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylhetemaryl groups, arylalkoxy groups, aryloxy groups, alkoxy groups, dialkylamino groups, -CONHAlk, -CONHAr, $-CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups; or R8 is R6-Ar_2-B-, in which B is a single bond or a connecting moiety; Ar_2 is an Ar_1 group; R6 is an R5 group; and which are useful in the treatment or prevention of e.g. obesity, depression, diabetes, bulimia etc.

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NOVEL METHOXYBENZAMIDE COMPOUNDS FOR USE IN MCH RECEPTOR RELATED DISORDERS

Field of the invention

The present invention relates to novel compounds that interact with a melanin-concentrating hormone receptor, a MCH receptor. The compounds have modulating activity on the MCH receptor such as e.g. antagonistic, agonistic or allosteric activity and are useful for medicinal or cosmetic purposes such as, e.g. in the treatment or prevention of feeding disorders like obesity, metabolic syndrome, Type II diabetes, bulimia etc. or in the treatment or prevention of depression.

The invention also relates to therapeutic and/or prophylactic use of the compounds, to processes for the preparation of the novel compounds, to pharmaceutical compositions comprising the compounds, to the manufacture of such compositions and to methods for the treatment and/or prevention of MCH receptor related disorders.

Background of the invention

Melanin-concentrating hormone (MCH) is a cyclic peptide that originally was isolated from salmoid pituitaries. In the fish, the 17 amino acid peptide causes aggregation of melanin and inhibits the release of ACTH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse and human exhibiting 100% amino acid identity. In the last decades there has been increasing activity in the research in the physiologic roles of MCH. It has been reported that MCH is involved in the feeding or body weight regulation, in energy balance, in response to stress, in water balance, in energy metabolism, in the general arousal/attention state, memory and cognitive functions and in psychiatric disorders. The biological effects of MCH are believed to be mediated by specific MCH receptors, and the MCH1 and MCH2 receptors have been described. Antagonists of MCH receptor (e.g. MCH1 receptor) may be suitable for use as obesity or weight reducing agents and they are also believed to have antidepressant and/or anxiolytic properties.

The present invention provides novel compounds that have a MCH modulating activity, i.e. antagonistic, inverse agonistic/negative antagonism, allosteric modulator, partial agonist or agonistic action.

Detailed description of the invention

In the present context the following definitions apply:

In the present context, the term "alkyl" is intended to indicate a branched or straight-chain, saturated chemical group containing 1-8 carbon atoms such as, e.g. 1-6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tert. butyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl *etc.*

The term "lower alkyl" is intended to indicate an alkyl group containing 1-6 carbon atoms, such as, .e.g, 1-4 carbon atoms, unless otherwise specified. Likewise, "lower alkenyl" and "lower alkynyl" are intended to indicate alkenyl and alkynyl groups, respectively containing 2-6 carbon atoms.

The term "alkenyl" is intended to indicate an unsaturated alkyl group having one or more double bonds and 2-8 carbon atoms unless otherwise specified.

The term "alkynyl" is intended to indicate an unsaturated alkyl group having one or more triple bonds and 2-8 carbon atoms unless otherwise specified.

The term "cycloalkyl" is intended to denote a cyclic, saturated alkyl group of 3-7 carbon atoms.

The term "cycloalkenyl" is intended to denote a cyclic, unsaturated alkyl group of 5-7 carbon atoms having one or more double bonds.

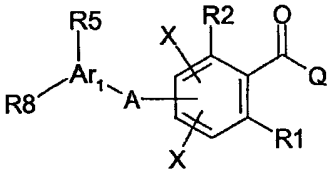
The term "alkoxy" is intended to indicate the group alkyl-O-.

The term "aryl" is intended to denote an aromatic (unsaturated), typically 6-membered, ring, which may be a single ring (e.g. phenyl) or fused with other 5- or 6-membered rings (e.g. naphthyl or indole).

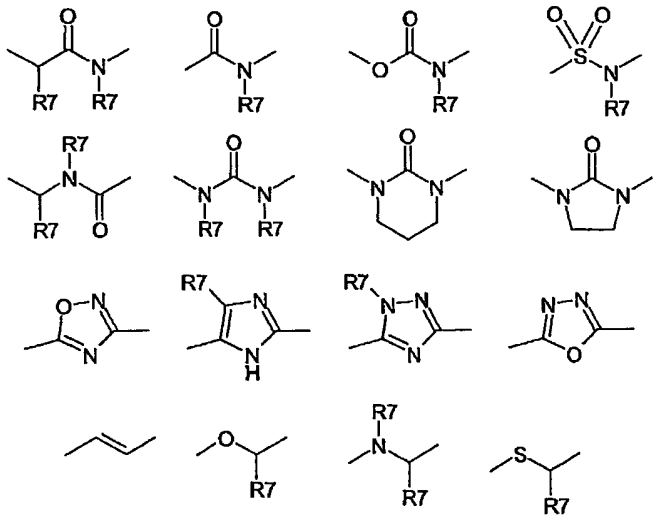
The term "heteroaryl" is intended to denote an aromatic (unsaturated), 5- or 6-membered, ring, which may be a single ring (e.g. pyridyl) or fused with other 5- or 6-membered rings (e.g. quinoline or indole).

The term "heterocyclyl" is intended to indicate a cyclic unsaturated (heteroalkenyl), aromatic ("heteroaryl") or saturated ("heterocycloalkyl") group comprising at least one heteroatom.

The present invention relates to a compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



and, wherein the linker -A- may be attached *via* either of the two free bonds to the Ar_1 group;

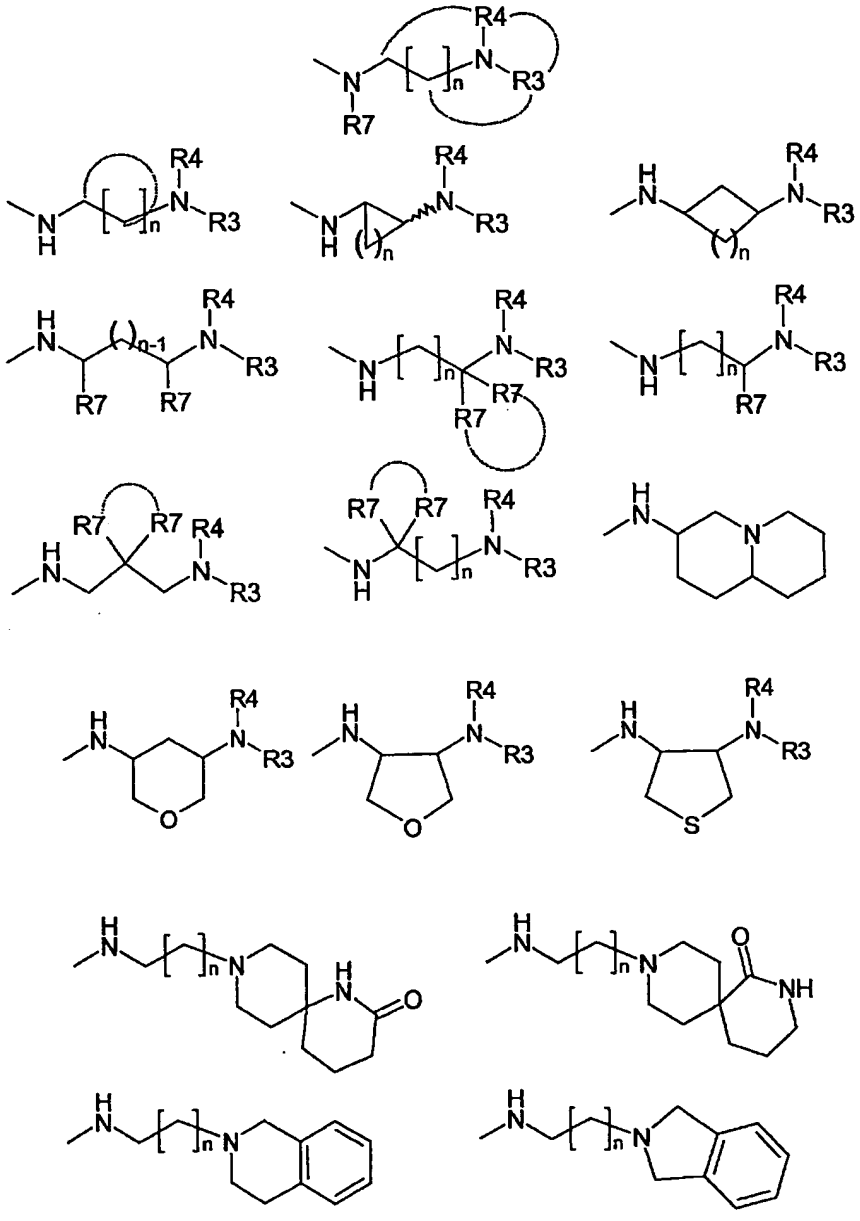
and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

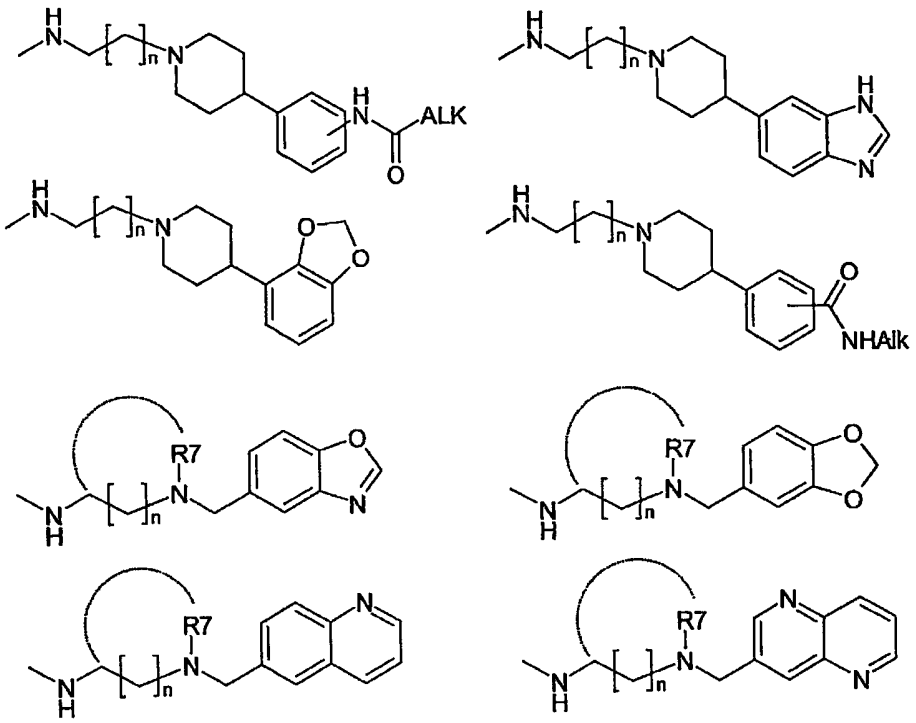
Ar_1 is an aryl or heteroaryl group such as, *e.g.* phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 is a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon,

R2 is an R1 group or hydrogen, an OH or an NH_2 group,

Q is selected from the group consisting of





R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbon atoms; alkylcycloalkyl with 4-9 carbon atoms; alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, -$CONH_2$, -CONHAlk, -$CONAlk_2$, aryl, substituted aryl, benzyl, substituted benzyl groups

Alk is the same or a different alkyl, alkenyl or alkynyl group;

R3 and R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

R5 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -SCH_3, partially or fully fluorinated alkyl,

alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2NAlk_2$, $-SO_2Alk$;

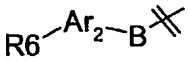
more than one R5 group, same or different, may be present on Ar_1; when more than one R5 or when one R5 and one R8 group are present they could be connected to each other, directly or with a suitable connecting moiety, to form rings;

X being the same or different H, F, Cl, Br, I, $-SCH_3$, $-CF_3$, $-OCF_3$, $-SCF_3$, OCH_3, or lower alkyl or alkenyl group;

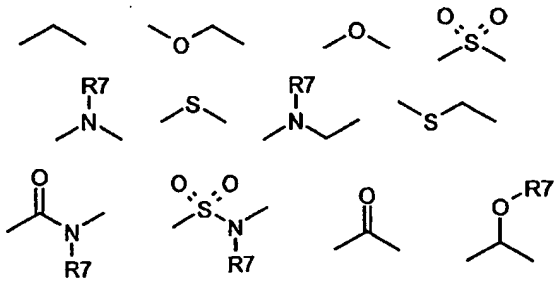
n is 1,2 or 3,

R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (*e.g.* $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr $-CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$;

or R8 has the structure



in which B is a single bond or a connecting moiety selected from the group consisting of:



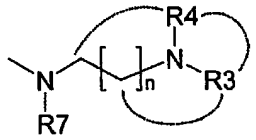
which may be attached *via* either of the two free bonds to the Ar_1 group;

Ar_2 is an aryl or heteroaryl group such as e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

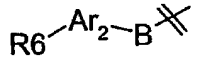
R6 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

more than one R6 group, same or different, may be present on Ar_2; when more than one R6 group is present they could be connected to each other to form rings.

In a specific embodiments Q is

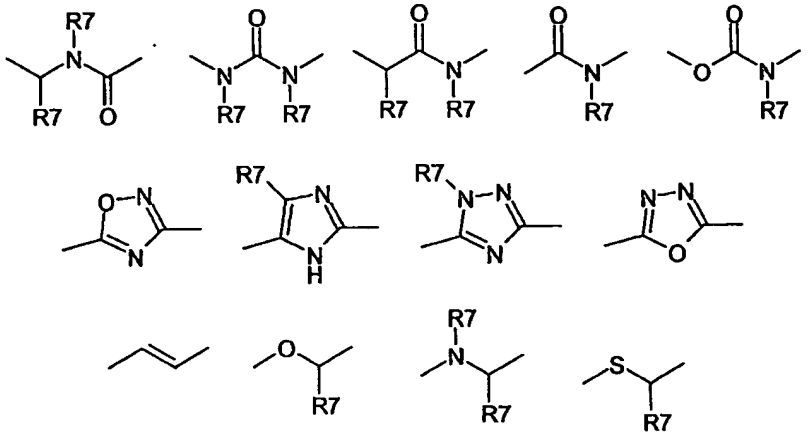


In another specific embodiment of the invention, R8 is



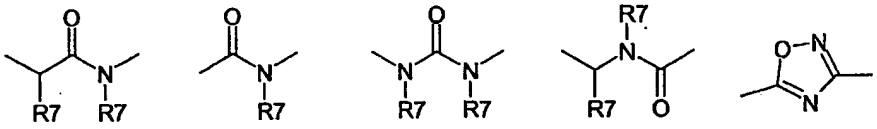
or, alternatively, R8 is selected from halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (*e.g.* $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -CF_3, -OCF_3, -SCF_3, SCH_3.

In further embodiments of the invention A is selected from the group consisting of:



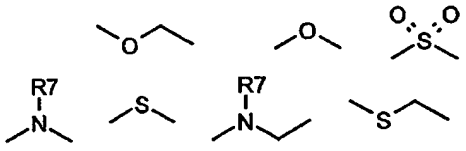
wherein R7 is as defined herein.

More specifically, A may be selected from the group consisting of:



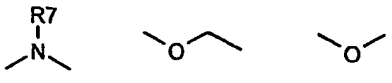
wherein R7 is as defined herein.

In those embodiments wherein B is present, it is a single bond or selected from the group consisting of:



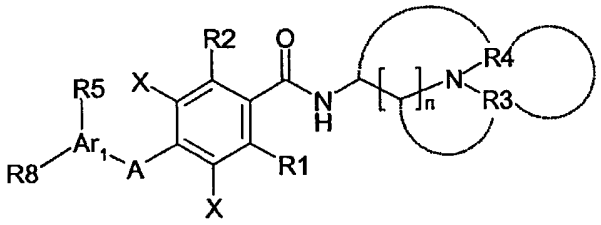
wherein R7 is as defined herein.

Alternatively, B is a single bond or is selected from the group consisting of:

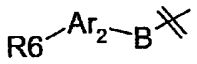


wherein R7 is as defined herein.

The invention also relates to a compound according to formula I with the following structure



wherein Ar_1, Ar_2, A, B, R1, R2, R3, R4, R5, R6, R7, R8, X and n are as defined herein In this embodiment interesting compounds are those, wherein R8 is

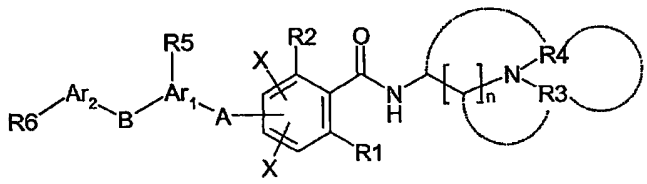


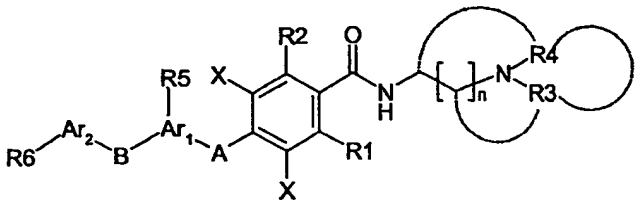
Normally, the -B- moiety is not placed ortho to the -A- linker.

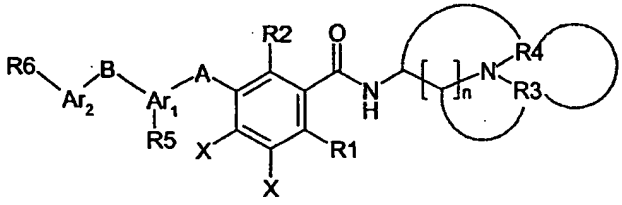
The invention also relates to a compound, wherein Ar_1 and Ar_2 are the same or different aryl or heteroaryl groups such as, e.g., phenyl, pyridine, thiophene, R2 may be hydrogen and/or X may be H, F, Cl, Br, I, CF_3, OCF_3, SCF_3, SCH_3 or lower alkyl or alkenyl group.

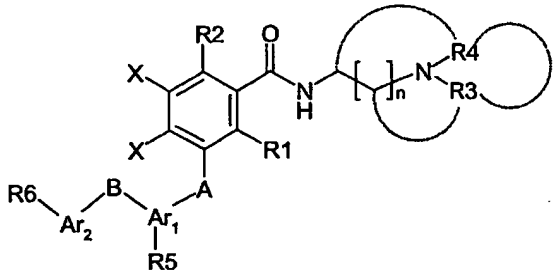
In another embodiment, R2 is H and X is H or F; R5 and R6 may be the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkyamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, $CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

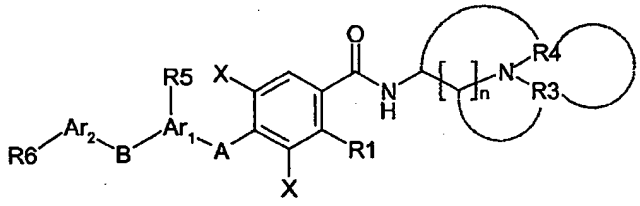
Other compounds according to the invention have the following formulas:

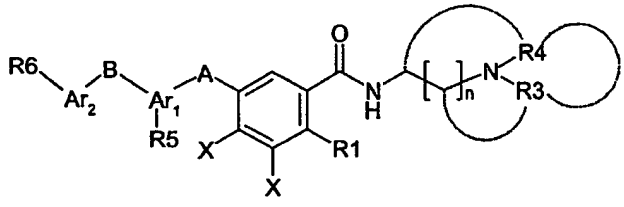


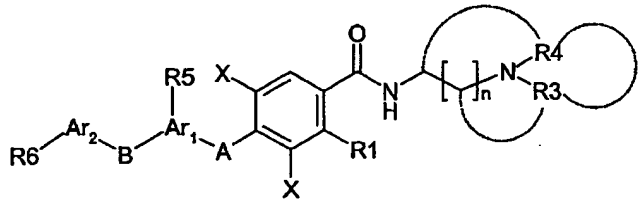


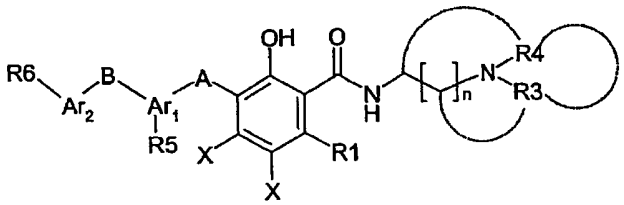


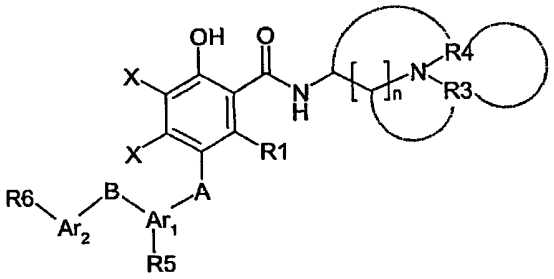


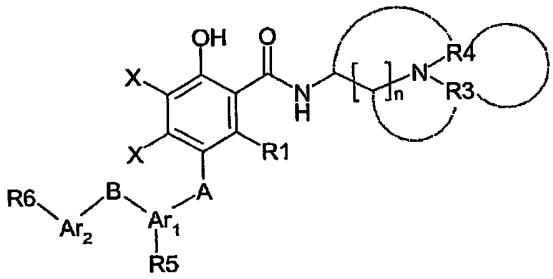


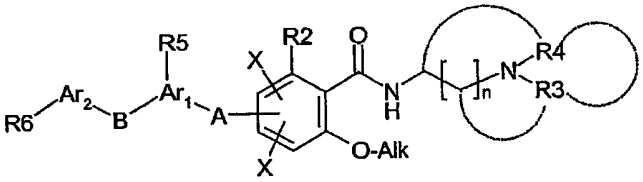


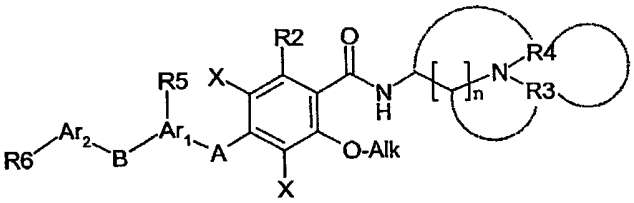


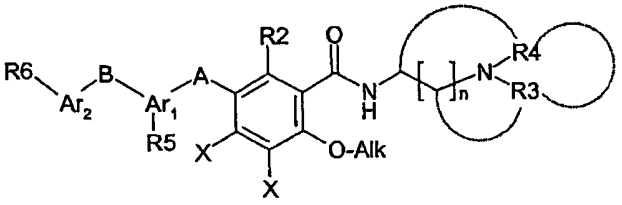


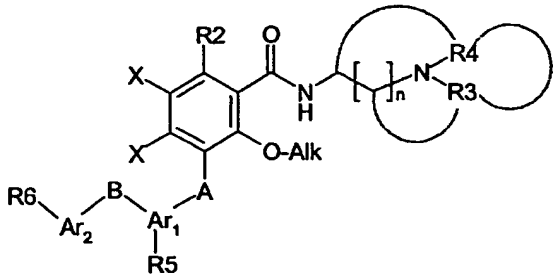










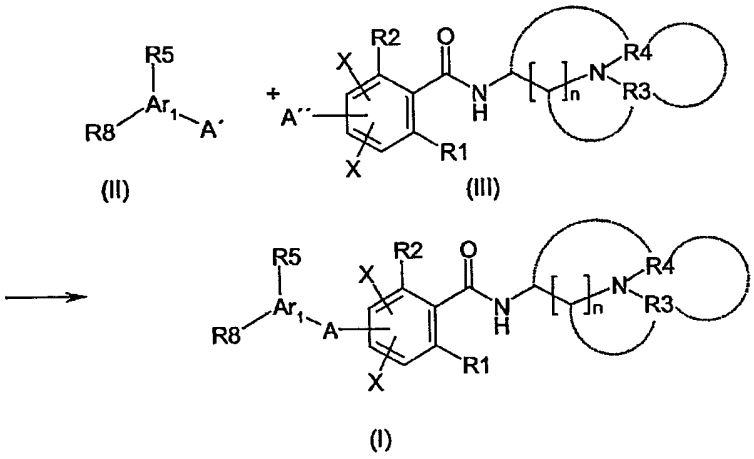

R2
O
X
N
H
R4
N
R3
n
X
O-Alk
R6
B
A
Ar2
Ar1
R5

Other specific embodiments appear from the appended claims and the examples herein.

Synthetic routes

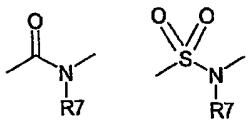
Synthetic routes

Compounds of formula I are preferably made by connecting an appropriately functionalised (A'') benzamide moiety III with a suitably functionalised (A') diaryl moiety II using well-known synthetic routes according to the following general scheme (Route 1):



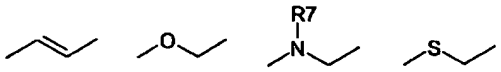
For example, urea bonds -A- can be formed by reaction of II having A' as isocyanate with III having A'' equal to NH-R7 using appropriate catalysis by base or acid. The reverse use of III having A'' as isocyanate with II having A' equal to NH-R7 can also be applied. Analogously, carbamates can for example be made by reaction of II having A' as isocyanate with III having A'' equal to OH or the reverse use of OH and isocyanate in A' and A''.

Preparation of amide and sulphonamide bonds



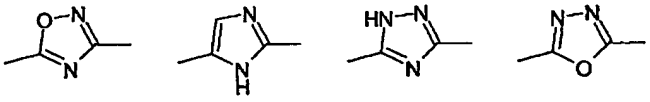
in the connecting A-linkage can be made via reaction of A'' in compound III being NH-R7 with activated forms, e.g. acid chlorides or active esters, of A' in compound II being COOH or SO_2OH. Alternatively, the conversion can be made directly with the acids having A' as COOH using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), and promoters such as 1-hydroxybenzotriazole. The reverse use of A' and A'' in II and III can be applied as well to form the linker in the opposite direction.

Formation of the connecting A-linkage to form

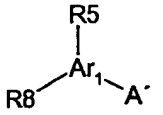


bonds in either direction between Ar1 and the benzamide can be made by N-, O- or S-alkylations of compound II with A' being OH, NH-R7, or SH with compound III with A'' being a CH_2-L wherein L being a suitable leaving group such as halogen (Cl, Br, I), tosyl or mesyl using appropriate catalysts and conditions. The alkene linkage can be made by a Wittig reaction with compound II with A' being CHO and compound III with A'' being CH_2-PPh_3. The reverse use of A' and A'' in II and III can be applied as well to form the linker in the opposite direction.

The 5-membered heterocyclic linkers



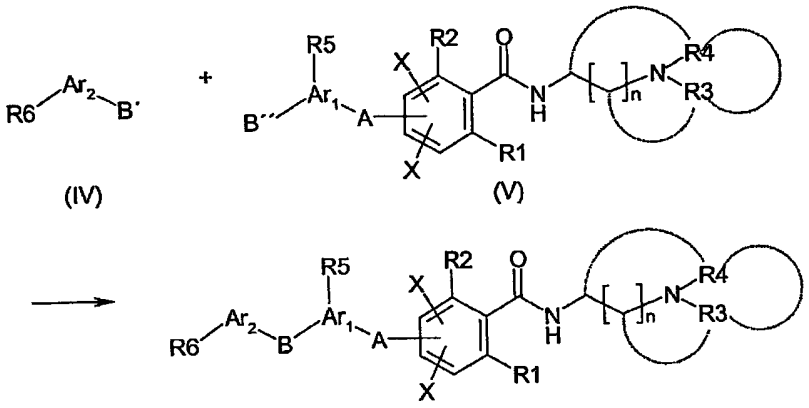
can be made according to standard cyclisation procedures using appropriate solvents, catalysts and temperatures. For example, formation of 1,2,4-triazole can be made from II with A' being acylhydrazide with III with A'' being amide or thioamide or the reverse orientation of A' and A''. 1,2,4-Oxadiazole can be formed from II with A' being amidoxime with III with A'' being carboxylic ester or the reverse orientation of A' and A''. 1,3,4-Oxadiazole can be formed from II with A' being acylhydrazide with III with A'' being carboxylic ester or the reverse orientation of A' and A''.



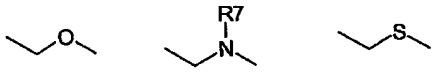
(II)

Aromatic substituents R4, R5 and R8 are preferably introduced prior to formation of the A- or B-linkage either direct or via a masked functionality that is compatible with the subsequent synthetic steps.

Alternatively, compounds of formula I are made by connecting an appropriately functionalised (B´´) arylated benzamide moiety V with a suitably functionalised (B´) aryl moiety IV using well-known synthetic routes according to the following general scheme (Route 2):



Thus, formation of the connecting B-linkage to form

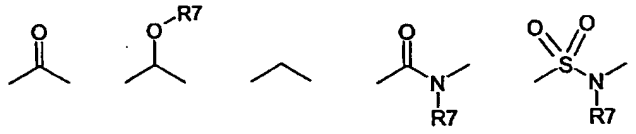


bonds in either direction between Ar1 and Ar2 can be made by N-, O- or S-alkylations of compounds IV having B´ as OH, NH-R7, or SH with compounds V having B´´ as CH_2-L, wherein L is a suitable leaving group such as halogen (Cl, Br, I), tosyl or mesyl using appropriate catalysts and conditions. The reverse use of B´ and B´´ in IV and V can be applied as well to form the linker in the opposite direction.

Formation of the connecting B-linkage to form

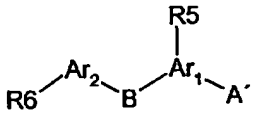
bonds can be made via coupling reactions of compounds IV with B' being OH, NH-R7, or SH with compound V having B'' as a suitable metal-reagent capable of forming the bond using appropriate catalysts and conditions or with B'' being a halogen that can be replaced under thermal or metal-catalysed conditions. The reverse use of B' and B'' in IV and V can be applied as well. The $-SO_2-$ linkage may be obtained by oxidation of the corresponding -S- derivative.

Formation of the connecting B-linkage to form



can be made by Friedel-Craft chemistry utilising compounds IV having B' as e.g. CO-Cl and compounds V having B'' as hydrogen to form the –CO- linkage followed by reduction to -CH(OH)-, that can be alkylated to give –CH(OAlk), or complete reduction to $-CH_2-$. The amide bond is made according to standard reactions involving compounds IV having B' as NH-R7 and activated derivatives of compound V with B'' being COOH or coupling reagents and promotors. The reverse use of B' and B'' in IV and V can be applied as well. The sulphonamides are made analogously from the corresponding SO_2-Cl derivatives and NH-R7 derivatives.

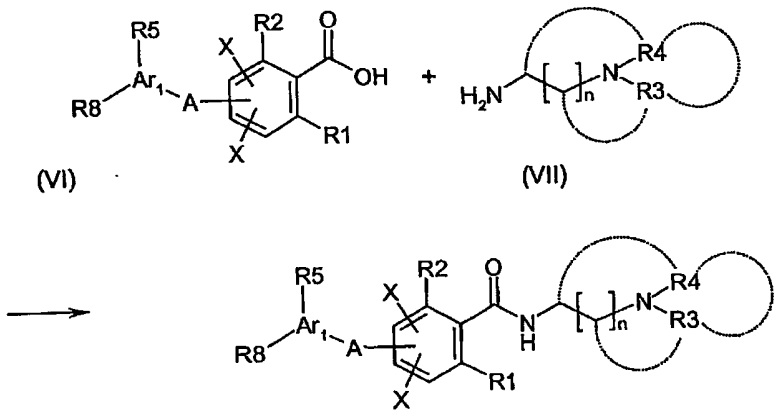
Notably, the -B- linkage is preferably introduced during the synthesis of intermediates II that are used in the coupling with III according to Route 1. In most cases the –B- linkage is made in compounds having A' groups that are compatible with the reaction conditions and that can be transformed into the required reactive moieties for subsequently forming the –A- linkage.



(II)

Aromatic substituents R4, R5 and R6 are preferably introduced prior to formation of the A- or B-linkage either direct or via a masked functionality that is compatible with the subsequent synthetic steps.

Compounds of formula I are also obtained by connecting carboxylic acid derivatives VI with amines VII using well-known synthetic routes according to the following general scheme (Route 3):



(VI) (VII)

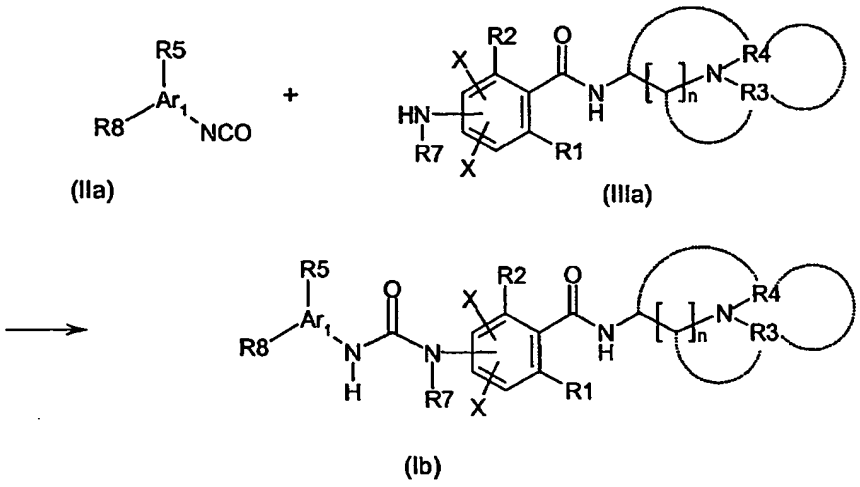
(I)

Thus, the benzamide bond is formed by reacting a suitably activated carboxylic acid VI (e.g. acid chloride) with the corresponding amines VII in the presence of a base or using suitable coupling reagents such as DCC in presence of promoting agents and a suitable base.

Alternatively, compounds of formula I can be made by N-alkylation of compounds of formula I having R3 and R4 being hydrogen using well-known synthetic routes such as reductive alkylation or alkylation with alkyl halides in case the functionalisation of the molecule is compatible with this type of reactions (Route 4).

Synthetic method 1A

Thus, compound (Ib) having NHCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.



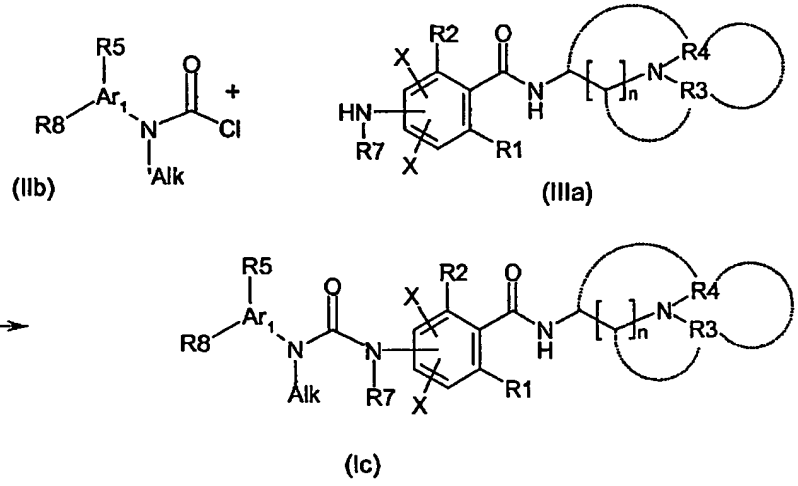
(IIa) (IIIa) (Ib)

Compound IIa and compound IIIa are reacted in an inert solvent in accordance with standard procedures. Typically, inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. Reaction temperature is usually room temperature and the reaction time is 2 hours to 1 day.

Compound IIa can be produced from the corresponding carboxylic acid. For instance, 4-phenoxyphenylisocyanate can be produced in accordance with methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley); R.C. Larock.

Synthetic method 1B

Compound Ic having N-AlkCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.



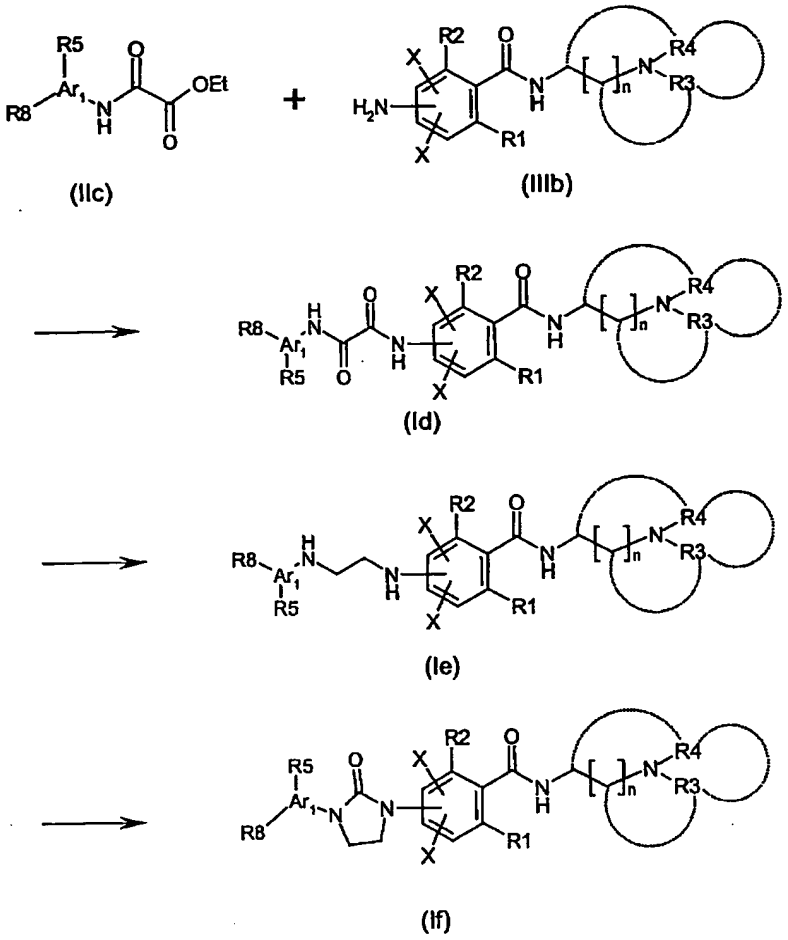
(IIb) (IIIa) (Ic)

Compound IIIa and 1 equivalent of compound IIb are reacted in an inert solvent in the presence of an excess of a base in accordance with known procedures (e.g. WO 9205174; *J.Med.Chem.* 43(20), 3653-3664, 2000). Suitable inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. As a base can be used for instance triethylamine, diisopropylethylamine and sodium carbonate. Typically, the reaction temperature is 0 °C to room temperature and the reaction time is 1 hour to 1 day.

Compound IIb can be produced from the corresponding N-alkyl aromatic amine by well-known methods. For instance, N-methyl-N-4-phenoxyphenylcarbamoyl chloride can be produced in accordance with methods such as described in *J. Labelled Compd. Radiopharma* 29(2), 149-155, 1991.

Synthetic method 1C

Compound If having 5-membered ring urea as linker A can be produced, for instance, by the following reaction sequence.

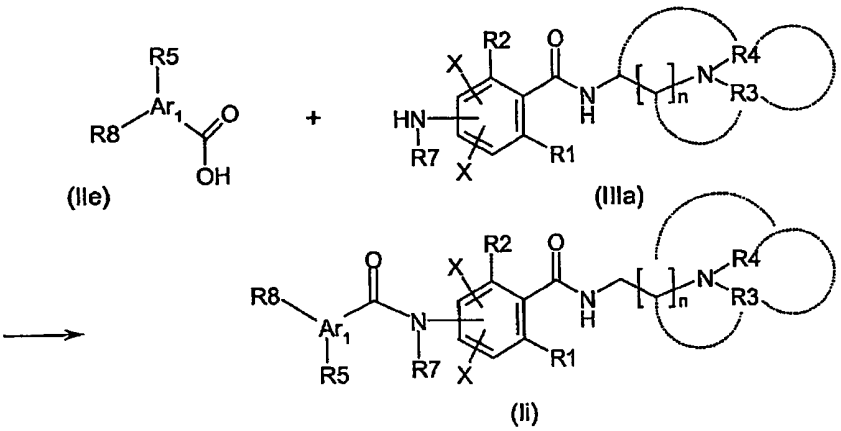


Compound Ie and 1 equivalent of carbonyldiimidazole are reacted in an inert solvent at elevated temperature until the reaction is completed. Typically, the reaction is conducted at reflux in acetonitrile for less than 24 hours.

Compounds IIc, Id and Ie can be produced following the functional group conversions described in procedures like the one in *J.Med.Chem.* 43(20), 3653-3664, 2000.

Synthetic method 1D

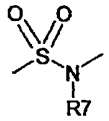
Compound Ii having CON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced by the following amidation reaction.



The amide bonds are formed by reacting a suitably activated carboxylic acid IIe (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) with anilines IIIa in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, 4-dimethylaminopyridine (DMAP) and sodium carbonate. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

The coupling can also be performed directly from IIe using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodiimide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, N-ethyldiisopropylamine, and 4-methylmorpholine. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

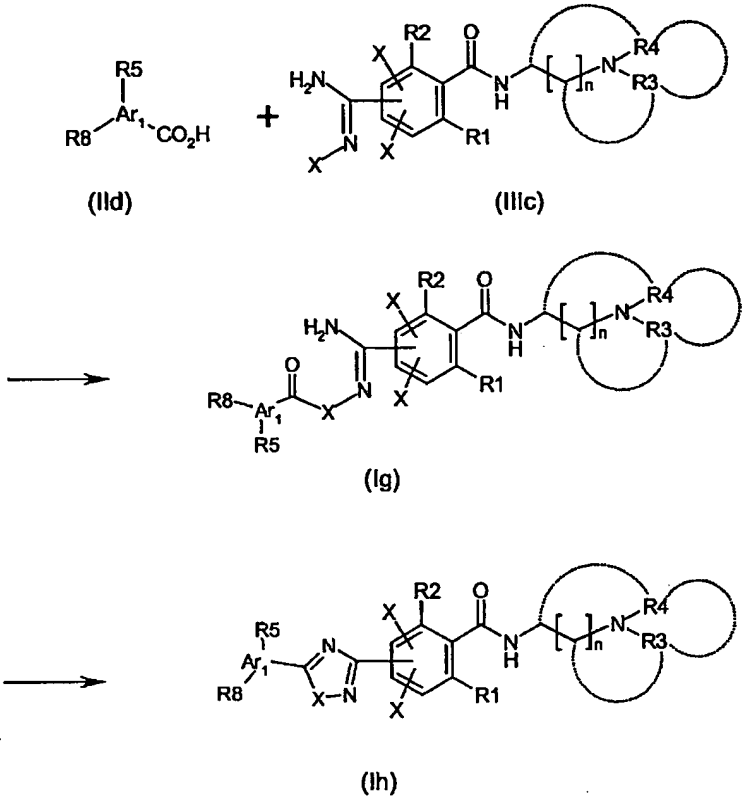
Analogously, a sulphonamide group, as the connecting A-linkage to form



bonds can be made via the corresponding reaction of Ar-NH-R7 (IIIa) with activated forms of sulphonic acids, such sulphonyl chlorides, in the presence of base.

Synthetic method 2

Compound Ih having 1,2,4-oxadiazole (X=O) or 1,2,4-triazole (X=NH) heterocyclic rings as linker A can be produced, for instance, by the following cyclodehydratation reaction.



(IId) (IIIc)

(Ig)

(Ih)

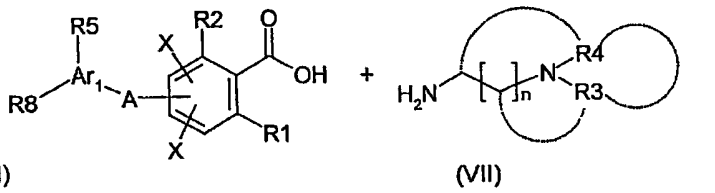
Compound Ig is reacted in an inert solvent with or without the presence of a suitable base or acid (e.g. N-tetrabutyl ammonium fluoride, sodium hydride, sodium ethoxide or polyphosphoric acid) in accordance with standard methods such as described in *Tetrahedron Lett.* 42, 1441-1443, 2001; *Tetrahedron Lett.* 42, 1495-1498, 2001. Suitable, inert solvents can be ether solvents, amide solvents and aromatic solvents. The reaction temperature is usually room temperature to 100°C and the reaction time is 1 hour to 3 days.

Compound Ig can be produced by reacting an activated derivative of compound IId with 1 equivalent of compound IIIc in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine and sodium carbonate.

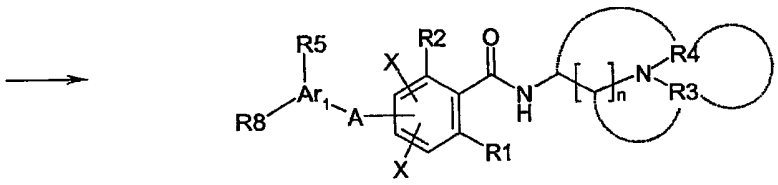
Appropriate examples of the activated derivatives of compound IId include active esters (e.g. esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinamide), acid chlorides, symmetrical or unsymmetrical anhydrides and orthoesters. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Compound IIIc can be produced from the corresponding amino compound IIIb by well known methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock; In "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky).

Synthetic method 3



(VI) (VII)



(I)

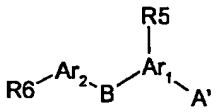
Benzamide bonds are formed by reacting a suitably activated carboxylic acid VI (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) with the corresponding amines VII in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, 4-dimethylamino-pyridine (DMAP) and sodium carbonate. . The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

The coupling can also be performed by using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodiimide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-

hydroxysuccinimide, 2-hydroxypyridine in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, N-ethyldiisopropylamine, and 4-methylmorpholine. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Synthetic method 4

Intermediates II



(II)

wherein A´ being groups that are compatible with the reaction conditions and that can be transformed into the required reactive moieties for subsequently forming the –A- linkage (e.g. $-CO_2H$, -NCO, -NAlkCOCl and $-NHCOCO_2Alk$) can be produced by firstly connecting Ar1 to Ar2 to each other in accordance with standard methods including N-, O- and S-alkylations and metal-catalysed cross couplings. One or several aromatic substituents R5 and R6, depending on their chemical properties, can be introduced either before or after the connection of Ar1 and Ar2 to each other.

Compounds II with B = -O-, -NH-R7-, or -S- are prepared from a suitable aryl halide and the corresponding phenol, aniline or thiol by heating with for example NaH or K_2CO_3 as base with the presence of a copper salt in DMF, pyridine or other high boiling solvents. An example of a metal assisted preparation of diaryl ethers is the coupling of a phenol with an arylbromide in the presence of $Pd(OAc)_2$ together with a phosphine ligand and K_3PO_4. For instance, 4-(4-chloro-phenoxy)benzoic acid can be produced in a two-steps synthesis from the corresponding 4-fluoro-acetophenone and 4-chlorophenol in accordance with methods such as described in *Synthesis*, 63-68, 1991 and *Eur. J. Med. Chem.*, 3, 205-214, 1984.

For compounds II with B equal to $-CH_2O-$, the preparation is performed by heating a benzyl halide and phenol with K_2CO_3 or NaOMe as base. These ethers can also be prepared from suitable benzyl alcohols and phenols utilising Mitsunobu conditions (DEAD and PPh_3). Compounds II with B equal to $-CH_2N$-R7- can be prepared from an aniline and a benzyl halide using K_2CO_3 as base. The corresponding thioether can be formed from a benzyl halide and thiophenol using KOH or NaOMe as bases and with for example ethanol as the solvent.

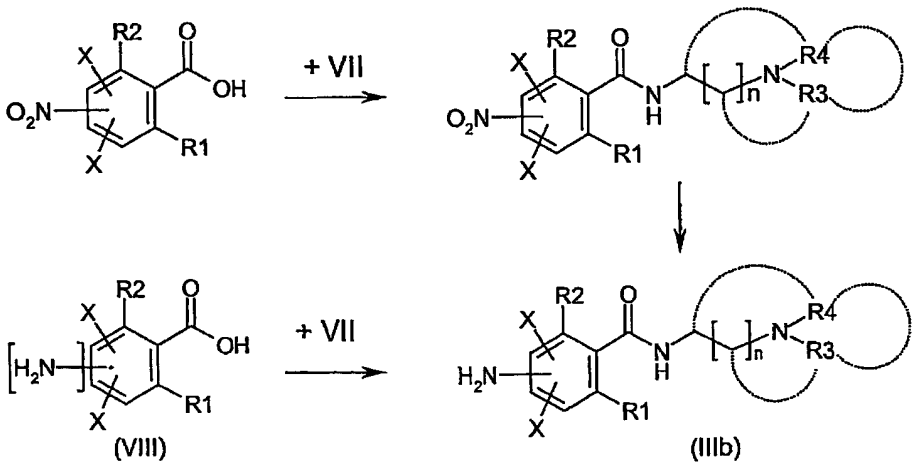
When B is equal to -CO- the compounds II can be synthesised from an arylic acid chloride either through a Friedel Craft reaction with an appropriate benzene derivative or via addition of a suitable Grignard reagent. Reduction of the same compound with $NaBH_4$ gives the compound II with B = -CH(OH)- that can be alkylated to produce –CH(OAlk)-. Utilising hydrogenation with PtO_2 as catalyst or Zn(Hg) as reducing agent yields compounds II with B = $-CH_2-$.

Compounds II with B = $-SO_2-$ can be prepared from the corresponding sulfide by oxidation with H_2O_2 or $KMnO_4$.

When B is an amide linkage compounds II can be prepared according to standard protocol from an activated carboxylic acid derivative (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) and an amine in an inert solvent and in the presence of a base. Suitable bases that can be used are triethylamine, diiisopropyl-ethylamine, pyridine, 4-dimethylaminopyridine (DMAP) and sodium carbonate. The coupling can also be performed by using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodimidmide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-hydroxysuccinimide, and 2-hydroxypyridine.

Synthetic method 5

Intermediate IIIb



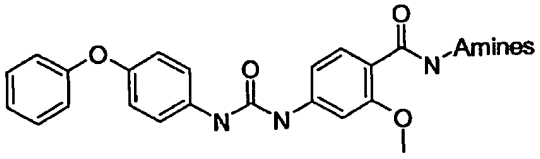
can be prepared by reacting an activated carboxylic acid derivative VIII according to methods described above, preferably having the aniline nitrogen suitably protected (e.g. Boc, CF_3CO), with the corresponding amine VII. The nitrogen may also be masked as a nitro group that subsequently is reduced to form IIIb. The N-alkylated derivative IIIa may be obtained via reductive alkylation of IIIb.

The carboxylic acids VIII are produced by well-known organic reactions including electrophilic substitutions or organometallic reactions such as ortho-lithiation and halogen-metal exchange followed by capture with electrophilic reagents. Alternatively, the aniline nitrogen may be introduced by a benzyne reaction.

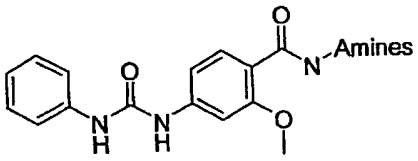
Compounds

Below follows some examples of specific compounds according to the invention. In the compounds mentioned, one part of the molecule such as e.g. the amine group, the linker –A-, the linker –B-, the Ar_1 or Ar_2 group, the R4, R5, R6 group or the chain length is varied, while the other parts are conserved. Though not shown nor specifically mentioned, the invention also includes all compounds wherein all variations in one part of the molecule, e.g. linker –A- is combined with all variations in another of the features, e.g. variation in the Ar_1 group.

Variation of the amine

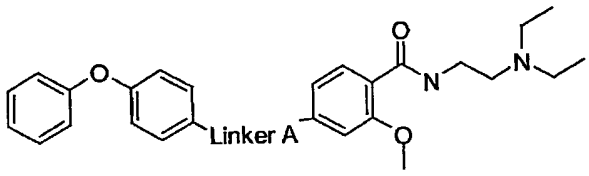


2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(3-pyrrolidin-1-yl-propyl)-benzamide,
N-(4-Dimethylamino-butyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,
N-(3-Dimethylamino-2,2-dimethyl-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,
N-(3-Dipropylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,



2-Methoxy-4-[3-phenyl-ureido]-*N*-(3-pyrrolidin-1-yl-propyl)-benzamide,
N-(4-Dimethylamino-butyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(3-Dimethylamino-2,2-dimethyl-propyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(3-Dipropylamino-propyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,

Variation of the linker A



N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(4-phenoxy-benzoyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-phenylacetylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(α-(4-phenoxy-phenyl)propanoylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(α-(4-phenoxy-phenyl)butanoylamino)-benzamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy- N^4-(4-phenoxy-phenyl)-terephthalamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy-N^4-methyl- N^4-(4-phenoxy-phenyl)-terephthalamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy- N^4-(4-phenoxy-benzyl)-terephthalamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy-N^4-methyl- N^4-(4-phenoxy-benzyl)-terephthalamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzenesulfonylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(4-phenoxy-benzenesulfonyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-phenylsulfamoyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[1,3-dimethyl-3-(4-phenoxy-phenyl)-ureido]-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(4-phenoxy-phenyl)-imidazolidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(4-phenoxy-phenyl)-tetrahydro-pyrimidin-1-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(4-phenoxy-phenyl)-4*H*-imidazol-2-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(4-phenoxy-phenyl)-1*H*-[1,2,4]triazol-3-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(4-phenoxy-phenyl)-2*H*-[1,2,4]triazol-3-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(4-phenoxy-phenyl)-5*H*-imidazol-4-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(4-phenoxy-phenyl)-vinyl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-phenoxymethyl)-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzyloxy)-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzylamino)-benzamide,

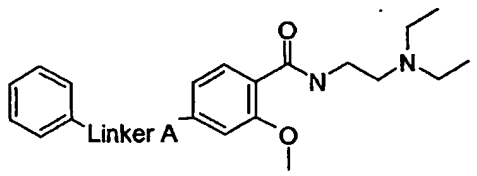
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(4-phenoxy-benzyl)-amino]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[(4-phenoxy-phenylamino)-methyl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-{[methyl-(4-phenoxy-phenyl)-amino]-methyl}-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-phenylsulfanylmethyl)-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzylsulfanyl)-benzamide



N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzoylamino)-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzoyl)-amino]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylacetylamino)-benzamide,

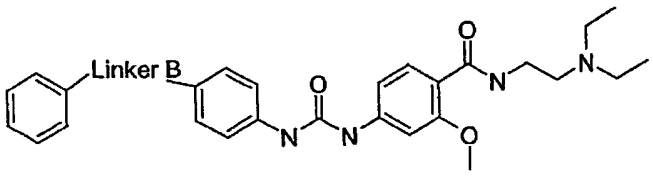
N-(2-Diethylamino-ethyl)-2-methoxy-4-(□-(phenyl)propanoylamino)-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-(□-(phenyl)butanoylamino)-benzamide,

N^1-(2-Diethylamino-ethyl)-2-methoxy- N^4-(phenyl)-terephthalamide,

N^1-(2-Diethylamino-ethyl)-2-methoxy-N^4-methyl- N^4-(phenyl)-terephthalamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy- N^4-(benzyl)-terephthalamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy-N^4-methyl- N^4-(benzyl)-terephthalamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzenesulfonylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzenesulfonyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylsulfamoyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[1,3-dimethyl-3-(phenyl)-ureido]-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(phenyl)-imidazolidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-methyl-3-(phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(phenyl)-tetrahydro-pyrimidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(phenyl)-[1,2,4]oxadiazol-5-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-4*H*-imidazol-2-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-1*H*-[1,2,4]triazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-[1,3,4]oxadiazol-2-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-2*H*-[1,2,4]triazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(phenyl)-5*H*-imidazol-4-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(phenyl)-vinyl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenoxymethyl)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzyloxy)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[(phenylamino)-methyl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{[methyl-(phenyl)-amino]-methyl}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylsulfanylmethyl)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzylsulfanyl)-benzamide

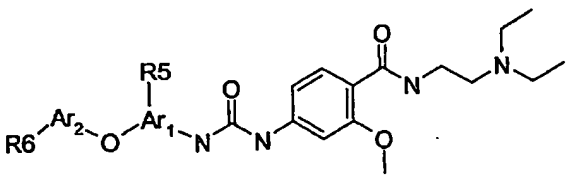
Variation of the linker B



4-[3-(4-Benzyl-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenylsulfanyl-phenyl)-ureido]-benzamide,

4-[3-(4-Benzenesulfonyl-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-[3-(4-Benzoyl-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(hydroxy-phenyl-methyl)-phenyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(methoxy-phenyl-methyl)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxymethyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenylsulfanylmethyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenylaminomethyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(3-{4-[(methyl-phenyl-amino)-methyl]-phenyl}-ureido)-benzamide,
4-[3-(4-Benzylamino-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(Benzyl-methyl-amino)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-[3-(4-Benzylsulfanyl-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-[3-(4-Benzyloxy-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-[3-(4-Benzoylamino-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(Benzoyl-methyl-amino)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenylcarbamoyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(methyl-phenyl-carbamoyl)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenylamino-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(methyl-phenyl-amino)-phenyl]-ureido}-benzamide.

Variation of the aromatic rings as well as their substituents



N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[5-(pyridin-3-yloxy)-pyridin-2-yl]-ureido}-benzamide,

4-(3-[2,2']Bipyridinyl-6-yl-ureido)-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(pyridin-3-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(pyrimidin-2-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-phenoxy-pyrimidin-5-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-phenoxy-pyrazin-2-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(thiophen-3-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(isothiazol-4-yloxy)-phenyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(oxazol-4-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(1*H*-pyrazol-4-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-phenoxy-thiophen-3-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-phenoxy-oxazol-4-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-oxazol-2-yl)-ureido]-benzamide,
4-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(3,4-Dichloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-Fluoro-3-chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(4-bromo-3-trifluoromethoxy-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(3,4-methylenedioxy-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(4-acetamido-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(3-hydroxymethyl-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(4-trifluoromethyl-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-(4-*p*-tolyloxy-phenyl)-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(3-fluoro-4-methoxy-phenoxy)-phenyl]-ureido}-benzamide,

N-(2-Diethylamino-ethyl)-4-{3-[4-(4-hydroxy-phenoxy)-phenyl]-ureido}-2-methoxy-benzamide, *N*-(2-Diethylamino-ethyl)-4-{3-[4-(4-dimethylamino-phenoxy)-phenyl]-ureido}-2-methoxy-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(4-methylamino-phenoxy)-phenyl]-ureido}-benzamide,

4-{3-[4-(4-Cyano-3-chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,

4-{3-[4-(4-Carbamoyl-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,

4-[3-(3-Chloro-4-phenoxy-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-fluoro-3-methoxy-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-bromo-6-methoxy-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-methylamino-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-hydroxymethyl-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-carboxamido-4-phenoxy-phenyl)-ureido]-benzamide,

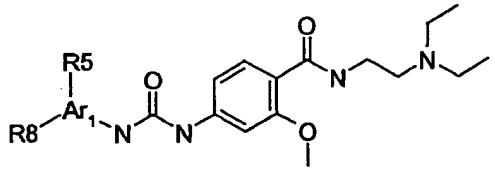
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-(*N*,*N*-dimethylcarboxamido)-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-methyl-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-3-trifluoromethoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-2-trifluoromethyl-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(4-trifluoromethoxy-phenoxy)-phenyl]-ureido}-benzamide



4-[3-(phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-indolyl)-ureido]-benzamide,

4-[3-(4-Benzofuranyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[3-pyridinyl]-ureido}-benzamide,
4-(3-[2,2']Bipyridinyl-6-yl-ureido)-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(pyridin-3-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-(8-quinolinyl)-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-phenoxy-pyrimidin-5-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-phenoxy-pyrazin-2-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-thiophenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-isothiazolyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-oxazolyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(1*H*-pyrazol-4-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-bromo-thiophen-3-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-chloro-oxazol-4-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifuoromethyl-oxazol-2-yl)-ureido]-benzamide,
4-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[3,4-Dichlorophenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-Fluoro-5-chlorothiophen-3-yl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-bromo-3-trifluoromethoxy-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[5-(3,4-methylenedioxy-phenoxy)-thiopen-3-yl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(4-acetamido-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-trifluoromethyl-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-(4-methyl-phenyl)-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-hydroxy-phenoxy)-phenyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-dimethylamino-phenoxy)-phenyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(4-methylamino-phenoxy)-phenyl]-ureido}-benzamide,
4-{3-[4-(4-Cyano-3-chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-Carbamoyl-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-[3-(3-Chloro-4-cyano-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-fluoro-3-methoxy-4-acetamido-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-bromo-6-methoxy-4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-hydroxymethyl-4-trifluoromethyl-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-carboxamido-4-iodo-phenyl)-ureido]-benzamide,

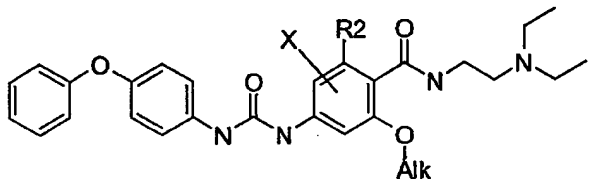
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-(*N,N*-dimethylcarboxamido)-4-chloro-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-trifluoromethyl-pyridin-2-yl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-trifluoromethoxy-thiophen-2-yl]-ureido}-benzamide,

Substituents on the benzamide moiety



N-(2-Diethylamino-ethyl)-2-ethoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

3-Chloro-*N*-(2-diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

3-Bromo-*N*-(2-diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

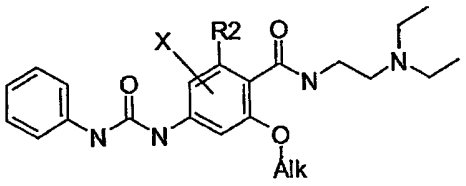
2-Amino-3-chloro-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

2-Amino-3-bromo-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

2-Amino-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2,6-dimethoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-3-trifluoromethyl-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-3-trifluoromethoxy-benzamide



N-(2-Diethylamino-ethyl)-2-ethoxy-4-[3-phenyl-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-benzamide,
3-Chloro-*N*-(2-diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-benzamide,
3-Bromo-*N*-(2-diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-benzamide,
2-Amino-3-chloro-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-phenyl-ureido]-benzamide,
2-Amino-3-bromo-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-phenyl-ureido]-benzamide,
2-Amino-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2,6-dimethoxy-4-[3-phenyl-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-3-trifluoromethyl-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-3-trifluoromethoxy-benzamide.

Salts, complexes or solvates

The invention also relates to physiologically acceptable salts, complexes, solvates or prodrugs of the compounds of the invention.

When a compound of the invention possesses a basic functional group it can form a salt with an inorganic or organic acid.

Examples of physiologically acceptable salts of the compounds according to the invention include salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid (to form e.g. a nitrate or a nitrite), sulfuric acid (to form e.g., a H_2SO_3 salt, a sulfate or a H_2SO_5 salt) and phosphoric acid (to form e.g. a H_3PO_3 salt or a H_3PO_4 salt)

Examples of salts with organic acids include salts with formic acid, acetic acid, propionic acid, butyric acid, pentanoic acid, oxalic acid, tartaric acid, malonic acid, succinic acid, citric acid, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, acrylic acid, malic acid, fumaric acid, H_2CO_3, lactic acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 3-chlorobenzoic acid.

Examples of salts with acidic amino acids include salts with aspartic acid and glutamic acid.

Optical isomers

When a compound of the invention contains optical isomers, diastereomers or other stereroisomers these are included as a compound of the invention as well as the racemate, i.e. mixture of enantiomers. Each of them can be obtained by methods known by a person skilled in the art. For example the optical isomer can be obtained using an optically active synthetic intermediate, an asymmetric synthesis or subjecting the racemic mixture of the final product or a suitable intermediate to optical resolution in accordance with known methods such as, e.g., fractional recrystallisation method, chiral column method, diastereomer method etc.

Other forms

The invention also encompasses a compound in amorphous, any polymorphous or any crystalline form.

Disorders

The compounds according to the invention can be used in medicine and modulate the activity of a MCH receptor. The compounds may be used as agents for preventing or treating diseases caused by or involving a melanin-concentrating hormone, i.e. they are

useful for treating or preventing a MCH or MCH receptor related disorder or abnormality in a subject such as, e.g., an animal or a mammal such as, e.g., a human.

The compounds according to the invention may have antagonistic, inverse agonistic, agonistic or allosteric activity against a MCH receptor, normally antagonistic activity.

In the present context an agonist is defined as a compound that increases the functional activity of a MCH receptor (e.g. the signal transduction through a receptor). The term "agonist" includes partial agonist, i.e. which increases the functional activity of the receptor to a submaximal level. An inverse agonist (or negative antagonist) is defined as a compound that decreases the basal functional activity of a MCH receptor. An allosteric compound is defined as a compound that enhances or diminishes the effects of other receptor ligands.

An antagonist is defined as a compound that decreases the functional activity of a MCH receptor either by inhibiting the action of an agonist or by its own intrinsic activity.

The MCH receptors mentioned in the invention include MCH1 and MCH2 receptors. It also includes MCH receptors having at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequences CTLITAMDAN or CTIITSLDTC.

The MCH receptors may be an animal or a mammalian or non-mammalian receptor, such as a human receptor.

Increasing or decreasing the activity of a MCH receptor such as, e.g. a MCH1 receptor alleviates a MCH-related disorder or abnormality. In specific embodiments the disorder is a steroid or pituitary hormone disorder, an epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, a muscoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as, e.g., Alzheimer's disease, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder such as, e.g. Parkinson's disease, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder such as, e.g. depression, a stress-related disorder, a fluid-balance disorder, a urinary

disorder such as, e.g., urinary incontinence, a seizure disorder, pain, psychotic behaviour such as, e.g., schizophrenia, morphine or opioid tolerance, opiate addiction or migraine.

More specifically, the compounds of the invention are useful for the treatment or prevention of feeding disorders such as, e.g., overweight, adiposity, obesity and bulimia (e.g. malignant mastocytosis, exogeneous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophyseal adposity, hypoplasmic obesity, hypophysal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity etc.), hyperfagia, emotional disorders, dementia or hormonal disorders.

In the present context the term body mass index or BMI is defined as body weight (kg)/height^2 (m^2), and the term overweight is intended to indicate a BMI in a range from about 25 to about 29.9, whereas obesity is intended to indicate a BMI, which is at least about 30.

A compound of the invention is also useful as an agent for preventing or treating lifestyle diseases such as, e.g., diabetes, diabetic complications (e.g. retinopathy, neuropathy, nephropathy etc.), arteriosclerosis and gonitis.

The present invention further relates to a cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to the invention

The invention also relates to a method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A mentioned above, the MCH-related disorders may be a feeding disorder. Accordingly, the invention relates to a method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

The invention also relates to a method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Furthermore, the invention relates to a method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Another aspect of the invention is a method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A still further aspect of the invention is a method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Pharmaceutical compositions

The compounds for use in the methods according to the invention are normally presented in the form of a pharmaceutical or a cosmetic composition comprising the specific compound or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

The compounds may be administered to the animal including a mammal such as, e.g., a human by any convenient administration route such as, e.g., the oral, buccal, nasal, ocular, pulmonary, topical, transdermal, vaginal, rectal, ocular, parenteral (including *inter*

alia subcutaneous, intramuscular, and intravenous), route in a dose that is effective for the individual purposes. A person skilled in the art will know how to chose a suitable administration route.

The pharmaceutical or cosmetic composition comprising a compound according to the invention may be in the form of a solid, semi-solid or fluid composition.

The solid composition may be in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, granulates, particulate material, solid dispersions or solid solutions.

A semi-solid form of the composition may be a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or a aerosol.

Fluid compositions, which are sterile solutions or dispersions can utilized by for example intraveneous, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection of infusion. The compounds may also be prepared as a sterile solid composition, which may be dissolved or dispersed before or at the time of administration using e.g. sterile water, saline or other appropriate sterile injectable medium.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be vagitories, suppositories, plasters, patches, tablets, capsules, sachets, troches, devices etc.

The dosage form may be designed to release the compound freely or in a controlled manner e.g. with respect to tablets by suitable coatings.

The pharmaceutical composition may comprise a therapeutically effective amount of a compound according to the invention.

The content of a compound of the invention in a pharmaceutical composition of the invention is e.g. from about 0.1 to about 100% w/w of the pharmaceutical composition.

The pharmaceutical or cosmetic compositions may be prepared by any of the method well known to a person skilled in pharmaceutical or cosmetic formulation.

In pharmaceutical or cosmetic compositions, the compounds are normally combined with a pharmaceutical excipient, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically or cosmetically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavours, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Dosage

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the composition, the route of administration, the frequency of administration, the age, weight, gender, diet and condition of the subject to be treated and the condition being treated and the advancement of the disease condition etc.

Suitable dosages may be from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

The amounts can be divided into one or several doses for administration daily, every second day, weekly, every two weeks, monthly or with any other suitable frequency. Normally, the administration is daily.

A compound or a pharmaceutical composition according to the invention may be used in combination with other drug substances such as agents for treating disorders like e.g. diabetes, diabetes complications, obesity, hypertension, hyperlipidemia, arteriosclerosis, arthritis, anxiety, and/or depression etc.

Experimental

Materials and methods

Transfections and Tissue Culture - The cDNA encoding the human MCH-1 receptor was cloned from a human brain cDNA library and cloned into the eukaryotic expression vector pcDNA3.1 (Invitrogen). Assays were performed on transiently transfected COS-7 cells or stably transfected CHO (Chinese Hamster Ovary) cells, expressing the human MCH-1 receptor in pcDNA3.1. Stable MCH-1 receptor transfectants of CHO cells were obtained using 5 μg plasmid cDNA and a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) with subsequent selection in 1 mg/ml G418 (Life Technology). Clones were screened by a MCH receptor radioligand binding assay (as described below). Stably transfected CHO cells were maintained in RPMI 1640 culture medium (Invitrogen), supplemented with 10 % fetal calf serum (Invitrogen), 100 U/ml penicillin, 100 μg/ml streptomycin (Life Technology), and 500 μg/ml G418 (Life Technology). COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 (Invitrogen) supplemented with 10 % fetal calf serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and were transiently transfected by a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) two days before assay.

Radioligand Binding Assay -Transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor were seeded in multi-well culture plates one day before the assay. The number of cells per well was determined by the apparent expression efficiency of the cell line aiming at 5 - 10 % binding of the added radioligand. Cells were assayed by competition binding for 3 hours at room temperature using 15 pM [^{125}I]-MCH (Amersham Pharmacia Biotech) plus variable amounts of unlabeled ligand in 0.5 ml of a 25 mM Hepes buffer, pH 7.4, supplemented with 10 mM $MgCl_2$, 5 mM $MnCl_2$, 10 mM NaCl, 0.1 % (w/v) bovine serum albumin (BSA), 100 μg/ml bacitracin. The assay was performed in duplicate. Nonspecific binding was determined as the binding in the presence of 1 μM MCH (Bachem). Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the dissociation and inhibition constants (K_d and K_i) were estimated from competition binding using the equations $K_d=IC_{50}-L$ and $K_i=IC_{50}/(1+L/K_d)$, respectively, where L is the concentration of radioligand.

Phosphatidylinositol assay - To assay phosphatidylinositol turnover, transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1

receptor ($2x10^5$ cells/well) were incubated for 24 h with 5 μCi of [^{3}H]-*myo*-inositol (Amersham Pharmacia Biotech) in 0.5 ml inositol-free culture medium. Cells were washed twice in PI-buffer: 20 mM HEPES, pH 7.4, supplemented with 140 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 1 mM $CaCl_2$, 10 mM glucose, 0.02% (w/v) bovine serum; and were incubated in 0.5 ml PI-buffer supplemented with 10 mM LiCl at 37 ^{0}C for 45 min. Phosphatidylinositol turnover was stimulated by submaximal concentrations of MCH, i.e. 10 nM in the presence of increasing amounts of ligand. The ligand was added 5 min. before adding the agonist (MCH). Cells were extracted with 10 mM ice-cold Formic acid, and the generated [^{3}H]-inositol phosphates were purified on Bio-Rad AG 1-X8 anion-exchange resin. Determinations were made in duplicate. PI data were analyzed and IC_{60} values determined by non-linear regression using the Prism software (GraphPad software, San Diego).

Scintillation Proximity Assay (SPA)– Measurement of [^{125}I]-MCHbinding was performed in duplicates by incubating membranes and beads with tracer in the presences of various concentrations of test compounds (10^{-8} to 10^{-4} M) in DMSO (3 µl) at room temperature for two hours. Membranes and beads were pre-incubated for 20 min. The binding buffer contained 50 mM Tris (pH 7.4), 8 mM MgCl2, 12% glycerol, 0.1% (w/v) bovine serum albumin (BSA), and protease inhibitors (Complete protease inhibitor cocktail tablets, Roche). A final [^{125}I]-MCH(2000 Ci/mmol; Amersham Pharmacia Biotech) concentration of 75.000 cpm/well (33.8 nCi) was applied and PEI-treated WGA-coupled PVT SPA beads, type B from Amersham Pharmacia Biotech were used at a final concentration of 0.4 mg/well. Moreover, CHO-K1 membranes expressing the hMCHreceptor were purchased from Euroscreen (ES-370-M) and a final concentration of 2µg/well were used. Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the inhibition constant (K_i) were estimated from competition binding using the equation $K_i=IC_{50}/(-1+L/K_d)$, where L and K_d are the concentration and affinity constant, respectively, of the radioligand.

In Vivo model measuring effects on food intake - The effects of test compounds on food intake were studied in male Sprague Dawley rats (290 – 325 g). The animals were individually housed in plexiglas cages (370 cm^2) at room temperature (21 ± 2 °C)and maintained on a 12 : 12h light – dark cycle (08.00 h – 20.00 h dark). They had free access to water; food (normal rat chow) was only available for the first 6 h of the dark period. The actual experiments studying food intake were conducted when the animals

were well accustomed to the housing conditions and feeding paradigm. At least a 10 – day acclimatization period was observed after entrance of the animals in the facilities.

At a day of an experiment, weight matched groups (n = 6-7) were injected with one of the test compounds (i.p. 10 mg/kg, dissolved in 10 % Tween 80), or the solvent (10 % Tween 80, 2 ml/kg). Cumulative food intake was registered over the 6-h feeding period. Results were analyzed by one-way ANOVA followed by post hoc Bonferroni test.

References:

Gether, U., Marray, T., Schwartz, T.W., and Johansen, T.E. (1992). Stable expression of high affinity NK_1 (substance P) and NK_2 (neurokinin A) receptors but low affinity NK_3 (neurokinin B) receptors in transfected CHO cells. *FEBS Lett.*, 296, 241-244.

Johansen, T.E., Schøller, M.S., Tolstoy, S. and Schwartz, T.W. (1990). Biosynthesis of peptide precursors and protease inhibitors using new constitutive and inducible eukaryotic expressions vectors. *FEBS Lett.*, 267, 289-294.

Examples

General comments:

A variety of unsymmetrically amines as in example 77 has been synthesised according to the following literature description, *Amundsen, L. H., Sanderson, J. J., Organic Syntheses, Vol.3, 256* Substitued diarylethers and diarylamines that has been used for urea couplings has been sythesised from arylhalides and phenols *(Buck, E., Song, Z. J., Tschaen, D., Dormer, P. G:, Volante, R. P., Reider, P. J., Organic Lett., 2002, 4, 1623)* or arylboronic acids and phenols or anilines *(Evans, D. A., Katz, J. L., West, T. R., Tetrahedron Lett. 1998, 39, 2937 and Chan, D. M. T., Monaco, K. L., Wang, R.-P., Winters, M. P., Tetrahedron Lett., 1998, 39, 2933.)*.

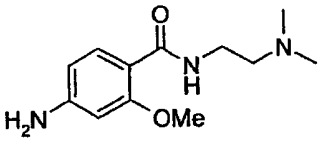
^{1}H NMR data are given either in full detailed or with characteristic selected peaks.
LCMS Conditions I: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 20% MeCN to 95% MeCN over 10 min, then 95% MeCN for 5 min. Negative ion scanning mode. Named; an20n15
LCMS Conditions II: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 20% MeCN to 95% MeCN over 10 min, then 95% MeCN for 5 min. Positive ion scanning mode. Named; an20p15

LCMS Conditions III: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 20% MeCN to 95% MeCN over 8 min, then 95% MeCN for 2 min. Positive ion scanning mode. Named; an20p10

LCMS Conditions IV: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 10% MeCN to 95% MeCN over 10 min, then 95% MeCN for 5 min. Positive ion scanning mode. Named; an10p15

Example 1

4-Amino-*N*-(2-dimethylamino-ethyl)-2-methoxy-benzamide

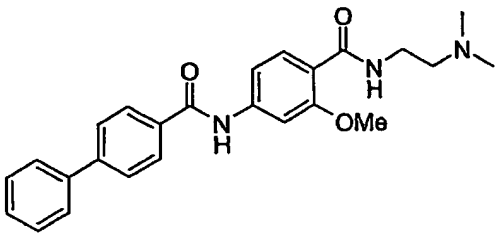


In a flask were placed 4-nitro-2-methoxybenzoic acid (0.50 g, 2.5 mmol) and dichloromethane (10 µl) under nitrogen atmosphere. The solution was cooled to 0°C, whereupon oxalyl chloride (0.20 µl, 2.3 mmol) and *N,N'*-dimethylformamide (2.0 µl) were added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 1h when potassium carbonate (0.25 g, 2.5 mmol) was added followed by addition of *N,N*-dimethylethylenediamine (0.30 µl , 2.5 mmol). The reaction mixture was stirred overnight before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated leaving 0.54 g (79 %) of *N*-(*N,N*-dimethylaminoethylamine)-4-nitro-2-methoxybenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H), 2.52-2.60 (m, 2H), 3.52-3.61 (m, 2H), 4.08 (s, 3H), 7.8-7.95 (m, 2H) and 8.29-8.37 (m, 1H).

To a solution of *N*-(*N,N*-dimethylaminoethyl)-4-nitro-2-methoxybenzoic amide (0.50 g, 1.87 mmol) in ethanol (10 µl) was Pd/C (40 mg, 20% w/w) added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a pad of celite and the filtrate was concentrated *in vacuo*. The crude product was chromatographed (Al_2O_3, dichloromethane/methanol/ammonia, 200:10:1) giving 0.42 g (95%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 6H), 2.52 (t, 2H), 3.52 (q, 2H), 3.87 (s, 3H), 6.19 (s, 1H), 6.32 (d, 1H), 7.98 (d, 1H) and 8.13 (br s, 1H).

Example 2

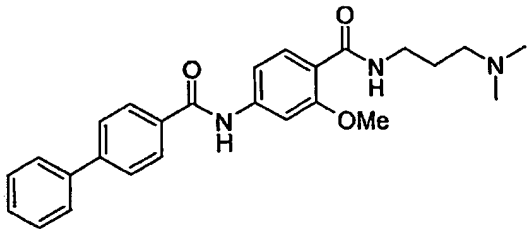
Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-3-methoxy-phenyl]-amide



4-phenyl-benzoic acid (0.35 g, 1.8 mmol) was dissolved in dichloromethane (10 µl) in an inert atmosphere and cooled to 0 °C, whereupon oxalyl chloride (140 µl,1.6 mmol) and *N,N'*-dimethylformamide (5 µl) were added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 1h when potassium carbonate (0.25 g, 1.77 mmol) was added. This solution was slowly added under inert atmosphere to **Ex 1** dissolved in dichloromethane (5 µl) and the reaction mixture was stirred overnight before extraction with EtOAc and Na2SO4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Al2O3, dichloromethane/methanol/ammonia, 200:10:1, followed by EtOAc/Heptane, 1:1) giving 10 mg (14%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 4.04 (s, 3H), 6.96 (d, 1H), 8.36 (br s, 1H).

Example 3

Biphenyl-4-carboxylic acid [4-(3-dimethylamino-propylcarbamoyl)-3-methoxy-phenyl]-amide



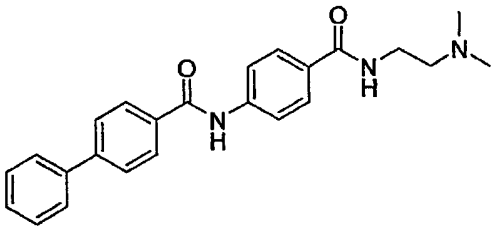
Following the same procedure as described in **Ex 1** was *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide prepared from 2-methoxy-4-nitrobenzoic acid (0.7 g, 3.55 mmol), oxalyl chloride (0.28 µl , 3.2 mmol), triethylamine (0.99 µl, 7.1 mmol) and 3-dimethylaminopropylamine (0.45 µl , 3.55 mmol) followed by reduction with Pd/C (0.04 g, 20% w/w) gave 0.67 g (75%) of *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (t, 2H), 2.24 (s, 6H), 2.36 (t, 2H),

3.49 (m, 2H), 3.90 (s, 3H), 4.02 (br s, 2H), 6.20 (s, 1H), 6.34 (d, 1H), 7.91 (br s, 1H) and 8.02 (d, 1H).

To a solution of 4-biphenylcarbonyl chloride (0.26 g, 0.80 mmol) in dichloromethane (5 µl) under inert atmosphere was a solution of the above prepared compound in dichloromethane (3 µl) added the reaction mixture was stirred at room temperature for three days. The purification was performed according to the protocol for preparation of **Ex 2** and the crude product was chromatographed (Al_2O_3, EtOAc/Heptane, 2:1) giving 0.10 g (30%) of the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (t, 2H), 2.30 (s, 6H), 2.44 (t, 2H), 3.55 (m, 2H), 4.04 (s, 3H), and 6.96 (d, 1H).

Example 4

Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-phenyl]-amide



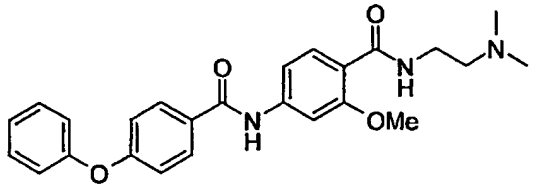
To a solution of 4-nitrobenzoyl chloride (0.50 g, 2.7 mmol) in dichloromethane (10 µl) were triethylamine (0.75 µl , 5.4 mmol) and *N,N*-dimethylethyldiamine added. The reaction mixture was stirred for three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was dissolved in ethanol (10 µl) and Pd/C (40 mg, 20 % w/w) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a celite pad and the filtrate was concentrated *in vacuo* giving 0.32 g (56%) of 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide.

To a solution of 4-biphenylcarbonyl chloride (0.47 g, 2.2 mmol) in dichloromethane (6 µl) under inert atmosphere were added triethylamine (0.4 µl , 2.9 mmol) and 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide (0.3 g, 1.45 mmol) dissolved in dichloromethane (3 µl). The reaction mixture was stirred at room temperature for three days. An additional portion of dichloromethane (3 µl) and PS-trisamine (0.8 g, 3.38 mmol/g) were added to the reaction mixture and the stirring was continued for 2 h at room temperature. The resin was filtered off and rinsed twice with dichloromethane (2 x 3 µL) before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica,

dichloromethane/methanol/ammonia, 100:10:1) and recrystillazed (EtOAc) giving 0.176 g (31%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 2.74 (t, 2H), 4.19 (t, 2H), 7.90 (d, 2H).

Example 5

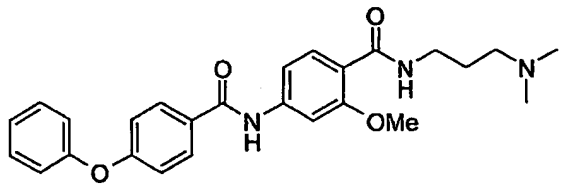
***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**



In a flask were placed 4-phenoxy benzoic acid (27 mg, 0.13 mmol) and *N,N*-dimethylformamide (2 μL) and the flask was cooled to 0°C, whereupon EDAC (24 mg, 0.13 mmol) and HOBt (17 mg, 0.13 mmol) were added. The mixture was gently stirred for 20 minutes at room temperature before **Ex 1** (41 mg, 0.19 mmol) dissolved in *N,N*-dimethylformamide and DiPEA (22 μl, 0.13 mmol) were added. The reaction was continuously stirred three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 12 mg (20%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 6H), 2.77 (m, 2H), 3.68 (m, 2H), 4.03 (s, 3H), 8.16 (d, 1H), and 8.39 (br s, 1H).

Example 6

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**

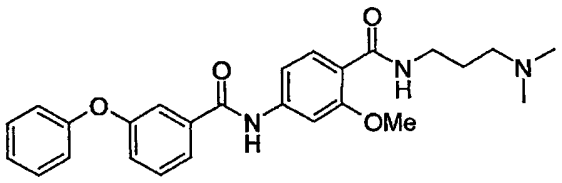


N-(*N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g), dichloromethane (15 μL), 4-phenoxy benzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N*-(*N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 μL). The solvent

was removed under vacuum giving the crude product. Chromatography (Silica, dichloromethane/methanol/ammonia, 200:10:1) yielded 8 mg (2%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.8 (dt, 2H), 2.28 (s, 3H), 2.42 (t, 2H), 3.53 (q, 2H), 4.02 (s, 3H), 6.91 (d, 1H) and 7.89 (d, 2H).

Example 7

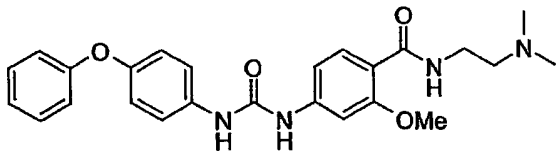
***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(3-phenoxy-benzoylamino)-benzamide**



N-(N,N)-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g), dichloromethane (15 µL), 3-phenoxybenzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 µL). The solvent was removed under vacuum giving the crude product. Chromatography (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 11 mg (3%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (dt, 2H), 2.28 (s, 3H), 2.42 (t, 2H), 3.54 (m, 2H), 4.00 (s, 3H), 6.92 (d, 1H) and 7.99 (d, 1H).

Example 8

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

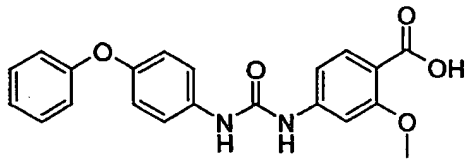


To a solution of **Ex 1** (30 mg, 0.13 mmol) in dichloromethane (2 µL) under nitrogen atmosphere was 4-phenoxyphenylisocyanate (64 µl, 0.30 mmol) added. The reaction was stirred for 2 h at room temperature, whereupon PS-trisamine (100 mg, 4.2 mmol/g). The suspension was gentle stirred over night. Methanol (20 µL) was added to dissolve some precipitation before the resin was filtered off and rinsed with dichloromethane (10 µL). The solvents were removed in vacuo and the crude product was purified through chromatography (silica, dichloromethane/ methanol/ammonia, 100:20:2) giving 24 mg

(42%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (t, 2H), 3.54 (m, 2H), 3.90 (s, 3H), 8.52 (s, 1H), 8.67 (s, 1H).

Example 9

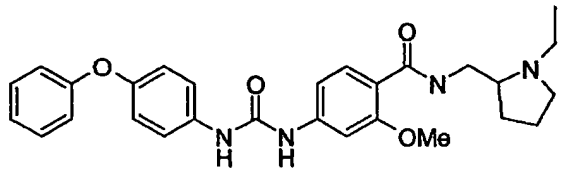
2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzoic acid



To a solution of 4-nitro-2-methoxybenzoic acid (5.0g, mmol) in ethanol (100 µL) was added Pd/C (200 mg, 20% w/w). The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a pad of celite and the filtrate was concentrated *in vacuo* giving 4-amino-2-methoxybenzoic acid. To a solution of 4-amino-2-methoxybenzoic acid (0.50 g, 3.0 mmol) in dichloromethane (10 µL) was added 4-phenoxyphenylisocyanate (0.65 µL, 3.6 mmol) under inert atmosphere. The reaction mixture was stirred for three days at room temperature and a precipitate was formed. Filtration gave 1.1 g (97%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.92-7.02 (m, 5H), 7.09 (t, 1H), 7.32-7.42 (m, 3H), 7.48 (d, 2H), 7.66 (d, 1H), 8.79 (s, 1H), and 9.03 (s, 1H).

Example 10

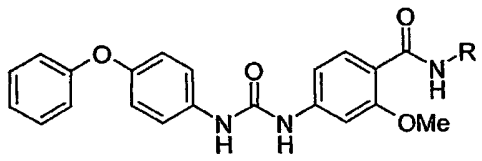
***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



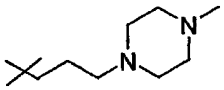
In a flask were placed **Ex 9** (57 mg, 0.15 mmol), HOBt (23 mg, 0.17 mmol), PS-DCC (0.15 g, 1.35 mmol/g), and dichloromethane (2 µL). The mixture was stirred at room temperature for 30 minutes, whereupon 2-aminomethyl-ethylpyrrolidine (0.10 mmol) was added. The reaction mixture was stirred over night. PS-trisamine (140 mg, 0.50 mmol) was added and stirring was continued for a day more. The resin was filtered off and rinsed with dichloromethane (3 x 2 µL). The solvent was removed *in vacuo* giving 35 mg (71%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H), 3.88 (s, 3H), 6.69 (d, 1H), 8.63 (t, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

Example 11-18

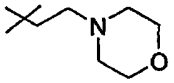
According to the procedure outlined in example 10 were the following compounds prepared utilizing **Ex 9** and the corresponding primary amines to the R-group;



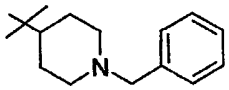
R =



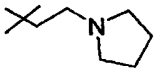
11



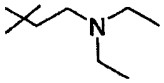
14



16



12



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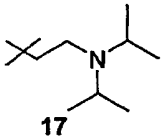
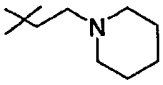
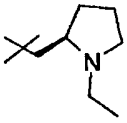


17



13



18

Example 11

2-Methoxy-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 1-(3-aminopropyl)-4-methylpiperazine was coupled giving 43 mg (82%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.60 (d, 1H), 8.69 (s, 1H), 9.02 (s, 1H).

Example 12

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide

Ex 9 and *N*-(2-aminoethyl)pyrrolidine was coupled giving 30 mg (63%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.72 (d, 1H), 8.44 (t, 1H), 8.85 (s, 1H), 9.13 (s, 1H).

Example 13

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-piperidin-1-yl-ethyl)-benzamide

Ex 9 and 1-(2-aminoethyl)piperidine was coupled giving 40 mg (81%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.64 (d, 1H), 7.06 (t, 1H), 7.95 (d, 1H), 8.58 (t, 1H), 8.76 (s, 1H), 9.03 (s, 1H).

Example 14

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 4-(2-aminoethyl)morpholine was coupled giving 18 mg (36%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H), 6.47 (d, 1H), 7.08 (t, 1H), 8.47 (s, 1H), 8.58 (t, 1H), 8.74 (s, 1H).

Example 15

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and *N,N*-diethyl-ethylendiamine was coupled giving 38 mg (78%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, 6H), 2.70 (q, 4H), 3.86 (s, 3H), 6.73 (d, 1H), 7.05 (t, 1H), 8.55 (t, 1H), 8.89 (s, 1H), 9.19 (s, 1H).

Example 16

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and 4-amino-1-benzylpiperidine was coupled giving 39 mg (70%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (s, 2H), 3.91 (s, 3H), 8.51 (s, 1H), 8.76 (s, 1H).

Example 17

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H), 8.82 (s, 1H), 9.09 (s, 1H).

Example 18
***N*-(1-Ethyl-pyrrolidin-2*R*-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and (*R*)-2-aminomethyl-ethylpyrrolidine was coupled giving 35 mg (71%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H), 3.88 (s, 3H), 6.69 (d, 1H), 8.63 (t, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

The following examples were prepared from **Ex 9** according to the same procedure as Ex 10-18

Example 19
***N*-(4-Benzyl-morpholin-2-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.49 (dd, 1H), 7.96 (d, 1H), 8.42 (t, 1H), 8.56 (s, 1H), 8.82 (s, 1H).

Example 20
***N*-(1-Benzyl-pyrrolidin-3-yl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 6.48 (dd, 1H), 8.40 (d, 1H), 8.60 (s, 1H), 8.87 (s, 1H).

Example 21
***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

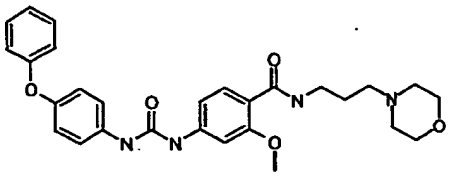
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, 6H), 3.84 (s, 3H), 9.51 (s, 1H), 9.88 (s, 1H).

Example 22
***N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.50 (dd, 1H), 8.65-8.70 (m, 2H), 8.56 (s, 1H).

Example 23

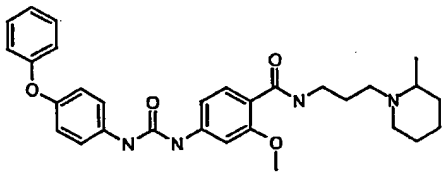
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82(m 2H), 2.42(m 6H), 3.46 (m 2H), 3.54 (m 4H), 3.68 (s 3H), 6.47 (dd 1H), 6.88-7.41 (m 9H), 7.90 (m 2H), 8.22 (m 1H), 8.58 (s 1H), 8,87 (s 1H).

Example 24

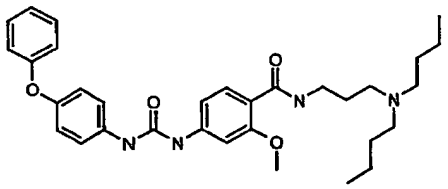
2-Methoxy-*N*-[3-(2-methyl-piperidin-1-yl)-propyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (m 4H), 1.42-4,0(m 14H), 3.86 (s 3H), 6.91-7.83 (m 12H), 8.21 (m 1H), 9.23 (s 1H), 9.61 (s 1H).

Example 25

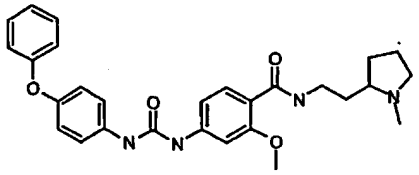
***N*-(3-Diethylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t 6H), 1.29 (m 4H), 1.59 (m 4H), 1.99 (m 2H), 2.82-2.95 (m 6H), 3.47 (m 2H), 3.87 (s 3H), 6.89-8.23 (m 13H), 9.17 (s H), 9.53 (s 1H).

Example 26

2-Methoxy-*N*-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–3.60 (m 14H), 3.85 (s 3H), 6.81-8.15 (m 13H), 8.99 (s 1H), 9.45 (s 1H)

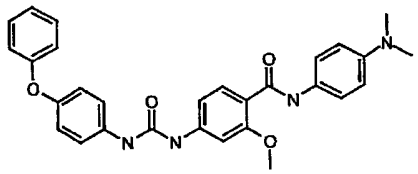
Example 27

***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 6H), 3.87 (t, 3H), 8.21 (t, 1H), 9.17 (s, 1H), 9.53 (s, 1H).

Example 28

***N*-(4-Dimethylamino-phenyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (s 6H), 4.06 (s 3H), 6.62-7.42 (m 14H), 8.12 (m 3H), 9.00 (s 1H), 9.79 (s 1H).

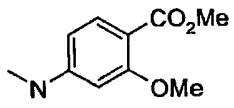
Example 29

***N*-(3-Dimethylamino-phenyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (s, 6H), 4.08 (s, 3H), 9.90 (s, 1H).

Example 30

2-Methoxy-4-methylamino-benzoic acid methyl ester

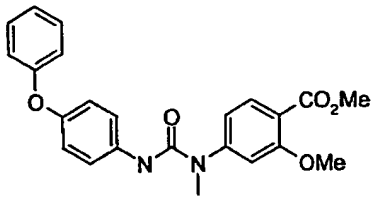


A solution of sodium methoxide (0.745g, 13.8 mmol), paraformaldehyde (0.124g, 4.14 mmol) and methyl 4-amino-2-methoxybenzoate (050g, 2.76 mmol) in methanol (40μL) was stirred overnight at 40°C before sodium borohydride (0.229g, 6.07 mmol) was added at room temperature. The resulting mixture was heated at 50°C for 8 hours. Methanol was removed *in vacuo*. The residue was partitioned between saturated aqueous NaHCO3 and dichloromethane. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3x20 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a crude solid which was

chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 : 95/4.5/0.5) to give the title compound as a white solid (0.278g, 1.43 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.30 (bs, 1H), 6.07 (s, 1H), 6.14 (d, 1H), 7.76 (d, 1H)

Example 31

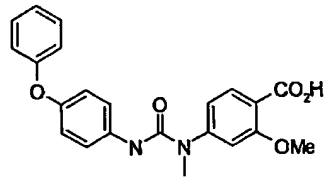
2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid methyl ester



The title compound **Ex 31** was obtained by carrying out the same procedure as in Example 8, using **Ex 30** and commercially available 4-phenoxyphenylisocyanate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.91 (s, 6H), 6.35 (s, 1H), 6.93-7.26 (m, 11H), 7.88 (d, 1H)

Example 32

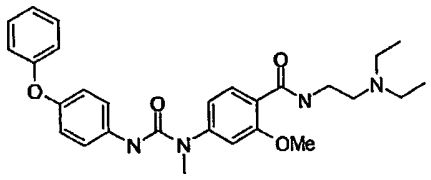
2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid



A solution of **Ex 31** (0.38g, 0.93 mmol) and lithium hydroxide (0.034g, 1.4mmol) in a THF/water mixture (2/1, 6μL) was stirred at 30°C for 3 days. After removal of the solvent *in vacuo*, the residue was diluted with water and washed with dichloromethane. The aqueous phase was then saturated with solid sodium chloride and acidified to pH = 1 with a 6N aq. HCl solution. The aqueous phase was extracted with dichloromethane. The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **Ex 32** as a white solid (0.249g, 0.63mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 3H), 4.09 (s, 3H), 6.52 (s, 1H), 6.93-7.33 (m, 11H), 8.20 (d, 1H)

Example 33

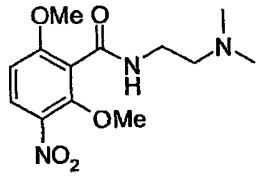
N-(2-Diethylamino-ethyl)-2-methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide



A solution of compound **Ex 32** (0.02 g, 0.051 mmol), EDAC (0.0146 g, 0.076 mmol) and HOBt (0.0089 g, 0.066 mmol) in dichloromethane (3 µL) was stirred at RT for 5 minutes before *N,N*-diethylethylenediamine (0.0086 µL) was added. The resulting reaction mixture was stirred at RT overnight, washed with saturated aq. NaHCO3 solution (3x), brine, dried over MgSO4 and concentrated *in vacuo*. The crude was chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 : 90/9/1) to give the title compound as a colourless oil which crystallised upon standing (0.025 g, 0.051 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 6H), 2.58 (q, 4H), 2.66 (t, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.97 (s, 3H), 6.36 (s, 1H), 6.91-7.32 (m, 11H), 8.29 (d, 1H), 8.35 (bs, 1H)

Example 34

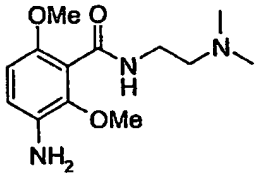
N-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-nitro-benzamide



A flask was charged with 2,6-dimethoxy-3-nitrobenzoic acid (1 g, 4.4 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.27 g, 6.6 mmol), hydroxybenzotriazole (772 mg, 5.72 mmol) and N,N-dimethylethylene diamine (0.48 µL, 4.4 mmol). Dichloromethane (50 µL) was added and the suspension was stirred under air for 16 h. The now clear reaction mixture was washed consecutively with water (2 x 20 µL) and brine (1 x 20 µL). The organic solution was then briefly dried over sodium sulfate before being filtered and reduced *in vacuo* to give *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-7.99 (2H, d), 6.77-6.72 (2H, d), 6.50-6.30 (1H, br s, NH), 3.97 (3H, s, MeO), 3.92 (3H, s, MeO), 3.60-3.45 (2H, m), 2.55-2.45 (2H, m), 2.25 (6H, s, Me_2N).

Example 35

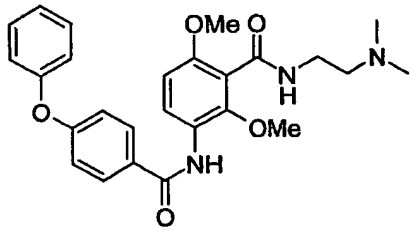
3-Amino-*N*-(2-dimethylamino-ethyl)-2,6-dimethoxy-benzamide



To a solution of *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide (1.31 g, 4.4 mmol) in dry methanol (50 µL) was added 10% palladium on carbon (50 mg). The reaction vessel was sealed and the atmosphere exchanged with nitrogen. The solution was then vigorously stirred and the atmosphere exchanged with hydrogen via a double balloon. Stirring continued for 16 h before the ballon was removed and the reaction mixture was filtered through a plug of celite (approx. 10 g). The residues were washed with excess methanol (approx. 100 µL) and the combined filtrates were reduced *in vacuo* returning a crude product which was chromatographed (Al_2O_3, dichloromethane-/methanol/triethylamine, 90:9:1) to give *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99-7.91 (1H, m), 6.72-6.67 (1H, m), 3.88 (3H, s, MeO), 3.85 (3H, s, MeO), 3.72-3.67 (2H, m), 3.13-3.05 (2H, m), 2.72 (6H, s, Me_2N).

Example 36

***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-(4-phenoxy-benzoylamino)-benzamide**

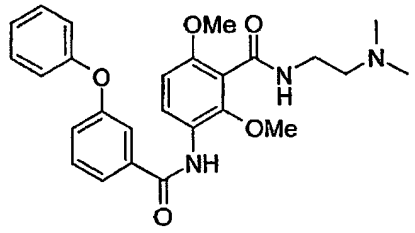


A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (8 mg, 32 µmol), hydroxybenzotriazole (5.6 mg, 46 µmol), *N,N*-dimethylaminopyridine (1 crystal) and 4-phenoxybenzoic acid (6.8 mg, 32 µmol). Dichloromethane (10 µL) was added and the solution was stirred under air before PS-DCC (60 mg, approx. 64 µmol) was added. Stirring continued for 72 h before PS-trisamine (200 mg) was added and the resulting suspension stirred for 3 h. The resins were removed by filtration and further washed with dichloromethane (50 µL) and the

combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 8.45-8.38 (1H, d), 8.40-8.30 (1H, br s, NH), 7.60-7.30 (5H, m), 7.22-7.12 (2H, m), 7.08-7.00 (1H, d), 6.74-6.55 (1H, d), 6.52-6.48 (2H, m, Ar-H + NH), 3.89 (3H, MeO), 3.83 (3H, MeO), 3.58-3.52 (2H, m), 2.54-2.48 (2H, m), 2.26 (6H, s, Me_2N).

Example 37

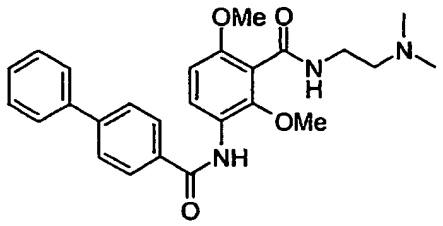
***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-(3-phenoxy-benzoylamino)-benzamide**



A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (80 mg, 0.32 mmol), hydroxybenzotriazole (43 mg, 0.32 mmol), *N,N*-dimethylaminopyridine (1 crystal) and 3-phenoxybenzoic acid (79 mg, 0.40 mmol). Dichloromethane (8 μL) was added and the solution was stirred under air before PS-DCC (350 mg, approx. 0.64 mmol) was added. Stirring continued for 72 h. Then PS-trisamine (100 mg) was added and stirred for 1 h before PS-iscocyanate (100 mg) was added and the resulting suspension stirred for a futher 1 h. The resins were removed by filtration and further washed with dichloromethane (50 μL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 8.42-8-38 (1H, d), 8.35-8.28 (1H, br s, NH), 7.48-7.35 (5H, m), 7.25-7.10 (2H, m), 7.08-7.10 (2H, d), 6.75-7.69 (1H, d), 6.68-6.48 (1H, br s, NH), 3.89 (3H, s, MeO), 3.83 (3H, s, MeO), 3.58-3.52 (2H, m), 2.53-2.49 (2H, m), 2.25 (6H, s, Me_2N).

Example 38

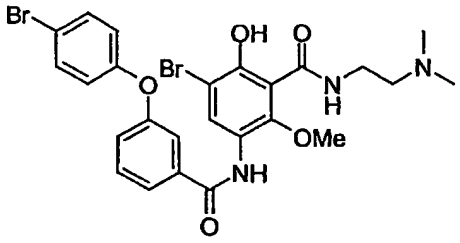
Biphenyl-4-carboxylic acid [3-(2-dimethylamino-ethylcarbamoyl)-2,4-dimethoxy-phenyl]-amide



A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (80 mg, 0.32 mmol), hydroxybenzotriazole (43 mg, 0.32 mmol), *N,N*-dimethylaminopyridine (1 crystal) and biphenylacetic acid (79 mg, 0.40 mmol). Dichloromethane (8 µL) was added and the solution was stirred under air before PS-DCC (350 mg, approx. 0.64 mmol) was added. Stirring continued for 72 h. Then PS-trisamine (100 mg) was added and stirred for 1 h before PS-iscocyanate (100 mg) was added and the resulting suspension stirred for a futher 1 h. The resins were removed by filtration and further washed with dichloromethane (50 µL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55-8.45 (1H, d), 8.45-8.35 (1H, br s, NH), 7.97-7.95 (2H, d), 7.80-7.70 (2H, d), 7.70-7.60 (2H, d), 7.60-7.40 (3H, m), 6.76-6.73 (1H, d), 6.60-6.50 (1H, br s, NH), 3.67 (3H, s; MeO), 3.86 (3H, s, MeO), 3.61-3.55 (2H, m), 256-2.52 (2H, m), 2.28 (6H, s, Me_2N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 165.1, 153.6, 147.8, 140.3, 134.0, 129.4, 128.5, 127.9, 127.6, 125.5, 122.4, 120.4, 120.4, 107.3, 62.7, 58.0, 56.6, 46.3, 45.5, 37.7.

Example 39

3-Bromo-5-[3-(4-bromo-phenoxy)-benzoylamino]-*N*-(2-dimethylamino-ethyl)-2,6-dimethoxy-benzamide

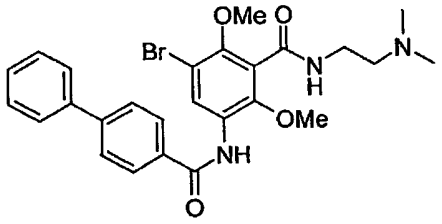


To a solution of **Ex 37** (120 mg, 0.26 mmol) in dichloromethane (10 µL) with acetic acid (1 drop) was added bromine (27 µL, 0.52 mmol) dropwise. The brown solution was then stirred for 16 h before a saturated solution of sodium thiosulfate (10 µL) was added and shaken to remove excess bromine. The organic solution was further washed with water (10 µL) and brine (10 µL) before being dried over sodium sulphate, filtered and reduced *in*

vacuo. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 9.10-9.00 (1H, br app s, NH), 8.88 (1H, s), 8.60-8.50 (1H, br s, NH), 7.64-7.60 (1H, dt), 7.57-7.56 (1H, t), 7.53-7.45 (3H, m), 7.21-7.18 (1H, dd), 6.98-6.93 (2H, d), 3.89 (3H, s, MeO), 3.58-3.53 (2H, q, CH_2NH), 2.59-2.57 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 40

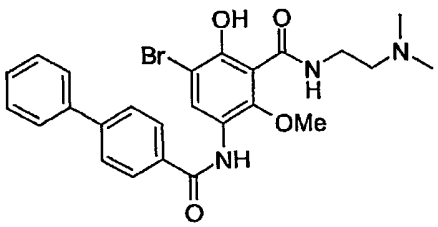
Biphenyl-4-carboxylic acid [5-bromo-3-(2-dimethylamino-ethylcarbamoyl)-2,4-dimethoxy-phenyl]-amide



To a solution of **Ex 38** (120 mg, 0.26 mmol) in dichloromethane (10 μL) with acetic acid (1 drop) was added bromine (27 μL, 0.52 mmol) dropwise. The brown solution was then stirred for 16 h before a saturated solution of sodium thiosulfate (10 μL) was added and shaken to remove excess bromine. The organic solution was further washed with water (10 μL) and brine (10 μL) before being dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 8.82 (1H, s), 8.50-8.60 (1H, br s, NH), 7.98-7.93 (2H, d), 7.77-7.72 (2H, d), 7.67-7.62 (2H, m), 7.58-7.35 (3H, m), 6.92-6.80 (1H, br s, NH), 3.96 (3H, s, MeO), 3.89 (3H, s, MeO), 3.64-3.59 (2H, q, CH_2NH), 2.65-2.58 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 41

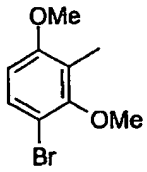
Biphenyl-4-carboxylic acid [5-bromo-3-(2-dimethylamino-ethylcarbamoyl)-4-hydroxy-2-methoxy-phenyl]-amide



From the above reaction a second product was isolated and identified as **Ex 41**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.07-9.04 (1H, br s, NH), 8.96 (1H, s), 8.75-8.65 (1H, br s, NH), 8.02-7.99 (2H, d), 7.76-7.73 (2H, d), 7.68-7.65 (2H, d), 7.60-7.35 (3H, m), 3.90 (3H, s, MeO), 3.59-3.54 (2H, q, CH_2NH), 2.58-2.54 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 42

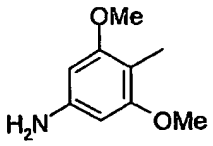
1-Bromo-2,4-dimethoxy-3-methyl-benzene



To a solution of 2,6-dimethoxytoluene (5 g, 33 mmol) in dichloromethane (100 µL) and acetic acid (1 drop) held at 0 °C was added bromine (1.67 µL, 33 mmol) dropwise. The pale brown solution was stirred for a further 5 h before being washed with a saturated solution of sodium thiosulfate (20 µL), sodium bicarbonate (20 µL), water (20 µL) and brine (20 µL). The organic solution was then dried over sodium thiosulfate, filtered and evaporated *in vacuo* to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.32 (1H, d), 6.56-6.53 (1H, d), 3.82 (3H, s, MeO), 3.81 (3H, s, MeO), 2.22 (3H, s, CH_3).

Example 43

3,5-Dimethoxy-4-methyl-phenylamine

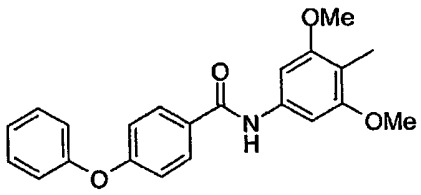


To a freshly prepared suspension of potassium amide (from potassium 12.87 g, 330 mmol) in liquid ammonia (300 µL) held at -78°C was added *example 9* (7.6 g, 33 mmol) dropwise over twenty minutes. The resulting suspension was stirred for a further 3 h and then excess potassium amide was quenched carefully with solid ammonium chloride (10 g) added portionwise over thirty minutes. Toluene (200 µL) was added and the liquid ammonia allowed to evaporate. The organic solution was then washed with water (3 x 100 µL) before being shaken with hydrochloric acid (6 N, 200 µL). The nascent precipitate was then collected by filtration and further washed with water (100 µL). The

residue was stirred with sodium hydroxide (10 N, 100 µL) for 1 h to form the free aniline, which was collected by filtration. The residues were washed with water (3 x 20 µL) and dried *in vacuo* to give the title compound.

Example 44

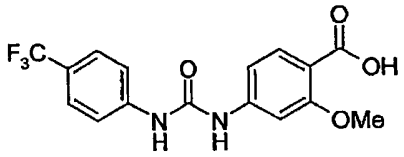
***N*-(3,5-Dimethoxy-4-methyl-phenyl)-4-phenoxy-benzamide**



A flask was charged with **Ex 43** (334 mg, 2 mmol), 4-phenoxybenzoic acid (471 mg, 2.2 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (573 m g, 3 mmol) and hydroxybenzotriazole (351 mg, 2.6 mmol). Dichloromethane (20 µL) was added and the suspension was stirred for 100 h. The now clear solution was washed with hydrochloric acid (1 N, 20 µL), sodium bicarbonate (20) and water (20 µL). The organic solution was dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 98:1:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.85 (2H, d), 7.75 (1H, s), 7.50-7.40 (2H, m), 7.25-7.15 (1H, m), 7.12-7.05 (4H, m), 6.93 (2H, s), 5.95 (1H, s), 3.85 (6H, s, MeO), 2.09 (3H, s, CH_3).

Example 45

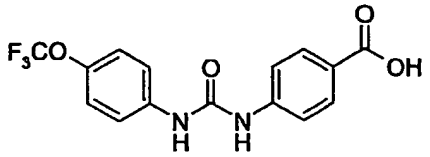
2-Methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzoic acid



To a solution of 4-amino-2-methoxybenzoic acid (3.4 g, 20.3 mmol) in dry dichloromethane (300 mL) under inert atmosphere was 4-trifluoromethylphenyl isocyanate (5.0 g, 26.7 mmol) added drop wise. The reaction was stirred over night at room temperature and a precipitate was formed during the reaction. The precipitate was filtered and washed with dichloromethane and gave 5.7 g (79 %) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 3.8 (s, 3H), 6.9 (dd, 1H), 7.4 (d, 1H), 7.4-7.7 (m, 5H), 9.2 (d, 2H), 12.2 (s, 1H). LCMS(an20n15); RT = 8.306 min, 352.9 m/z

Example 46

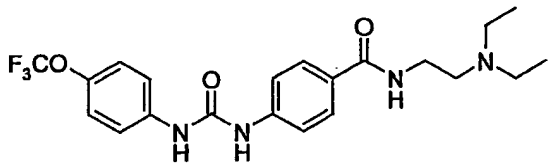
4-[3-(4-Trifluoromethoxy-phenyl)-ureido]-benzoic acid



Using the same procedure as described above was the title product synthesised from 4-amino-benzoic acid (1.2 g, 7.6 mmol) and 4-trifluoromethoxyphenyl isocyanate (2.0 g, 9.8 mmol) giving 2.7 g (quant.) of the product.
LCMS(an20n15); RT = 7.503 min, 338.8 m/z.

Example 47

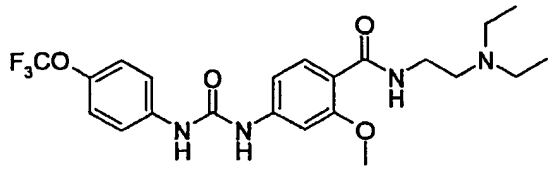
***N*-(2-Diethylamino-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**



To a solution of procainamide (26 mg, 0.112 mmol) in dichloromethane (1.5 mL) under inert atmosphere were triethylamine (31 μL) and 4-trifluoromethoxyphenyl isocyanate (30 μL, 0.145 mmol) added. The reaction was stirred for three days. PS-Trisamine (0.16 g, 3.58 mmol/g, 0.56 mmol) was added and the reaction was stirrede for two more days. The resin was filtered off and the reaction mixture was concentrated *in vacuo*. The crude product was purified by acidic ion exchange chromatography (SCX-colon) giving 29 mg (59%) of the title product. LCMS (an20p10): RT = 5.52 min, (M-1) = 439.0 m/z.

Example 48

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

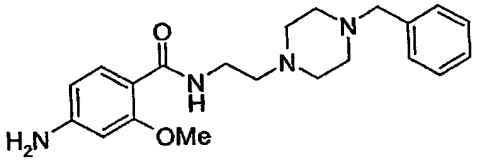


To a solution of 2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzoic acid (example 153) (50 mg, 0.135 mmol) in dichloromethane (3.5 mL) and dimethylformamide (0.35 mL) was added to polystyrene-DCC (0.5 g, 1.27 mmol/g, 0.64 mmol). Thereafter were HOBT (40 mg, 0.30 mol) and N^1,N^1-diethyl-ethyldiamine (18 μL, 16.5 mg 0.14 mmol) added and

the reaction was stirred over night. The resin was filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 12 mg (18%) of the title product. LCMS (an20p10): RT = 4.95 min, (M+1) = 469.0 m/z.

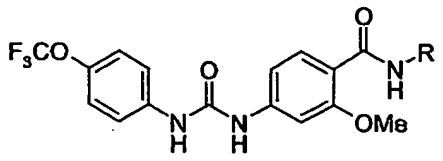
Example 49

4-Amino-*N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-2-methoxy-benzamide

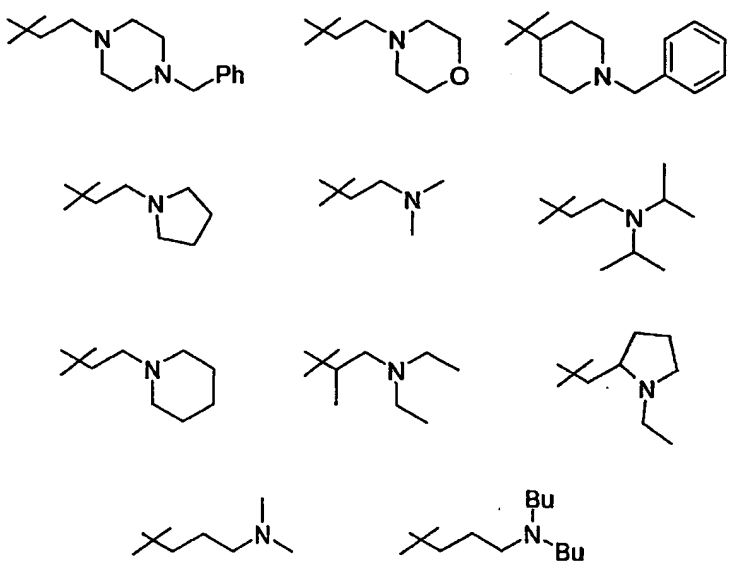


To a solution of 2-(4-Benzyl-piperazin-1-yl)-ethylamine (10 g, 45 mmol) in dry dichloromethane (500 mL) were EDC (11.3 g, 58 mmol), 2-methoxy-4-nitro-benzoic acid (11 g, 55 mmol) and HOBt (7.6 g, 56 mmol) added. The reaction mixture was left stirring at room temperature for four days. To the reaction was dichloromethane (3 L) added which was washed with Na2CO3 (sat.) (0.5 L). and the water phase was extracted with dichloromethane (3 L). The combined organic phases were dried (MgSO4), and concentrated *in vacuo*. The crude product (30 g) was chromatographed (silica, EtOAc/Heptane/triethylamine, 60:33:7) giving 17 g of 4-nitro-*N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-2-methoxy-benzamide (96 %). The product (4.3 g, 10.7 mmol) was dissolved in methanol (430 mL) and 5 % Pt/C (430 mg) was added under a nitrogen flow. The mixture was stirred in an H_2 atmosphere over night. The catalyst was filtered off using a pad of celite and the remaining solution was concentrated *in vacuo* giving 3.5 g (89%) of the title product. LCMS (an20p15); RT = 2.73 min, (M+1) = 369.

According to the procedure outlined in example 48 were the following compounds prepared utilizing **Ex 138** and the corresponding primary amines to the R-group, if not noted otherwise;



R =



Example 50

***N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

To a solution of 4-Amino-*N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-2-methoxy-benzamide (example 49) (60 mg, 0.163 mmol) in dichloromethane (2 mL) was 4-trifluoromethoxyphenyl isocyanate (45 mg, 0.22 mmol) added and the reaction was stirred under inert atmosphere over weekend. PS-Trisamine (100 mg, 3.58 mol/g) was added and the reaction mixture was continuously stirred over night. The resin was filtered off and washed twice with dichloromethane. The solvent was removed *in vacuo*. The crude product was purified through acidic ion exchange chromatography (SCX-colon) and as eluent was dichloromethane followed with methanol used. From the methanol was isolated 27 mg of the title product. LCMS(an20p15); RT = 6.61 min, (M+1) = 572.1

Example 51

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 138 and 3-Morpholin-4-yl-ethylamine were coupled giving 11 mg (16%) of the title product. LCMS(an20p15); RT = 5.99 min, (M+1) = 483.0.

Example 52

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and 1-Benzyl-piperidin-4-ylamine were coupled giving 11 mg (46%) of the title product. LCMS(an20p15); RT = 5.90 min, (M+1) = 543.0.

Example 53

2-Methoxy-*N*-(2-pyrrolidin-1-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 138 and 2-Pyrrolidin-1-yl-ethylamine were coupled giving 12 mg (19%) of the title product. LCMS(an20p15); RT = 8.22 min, (M+1) = 467.0

Example 54

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and N^1,N^1-Dimethyl-ethane-1,2-diamine were coupled giving 7.8 mg (13%) of the title product. LCMS(an20p15); RT = 5.91 min, (M+1) = 440.9

Example 55

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and N^1,N^1-Diisopropyl-ethane-1,2-diamine were coupled giving 17 mg (26%) of the title product. LCMS(an20p15); RT = 7.92 min, (M+1) = 497.0

Example 56

2-Methoxy-*N*-(2-piperidin-1-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 138 and 2-Piperidin-1-yl-ethylamine N^1,N^1-Diethyl-propane-1,2-diamine were coupled giving 12 mg (18%) of the title product. LCMS(an20p15); RT = 8.53 min, (M+1) = 481.0

Example 57

***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and N^1,N^1-Diethyl-propane-1,2-diamine were coupled giving 9.2 mg (14%) of the title product. LCMS(an20p15); RT = 6.17 min, (M+1) = 483.0

Example 58

***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and C-(1-Ethyl-pyrrolidin-2-yl)-methylamine were coupled giving 12 mg (19%) of the title product. LCMS(an20p15); RT = 7.52 min, (M+1) = 481.0

Example 59

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and N^1,N^1-Dimethyl-propane-1,3-diamine were coupled giving 12 mg (20%) of the title product. LCMS(an20p15); RT = 5.93 min, (M+1) = 455.0

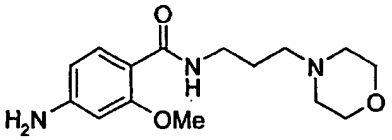
Example 60

***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 138 and N^1,N^1-Dibutyl-propane-1,3-diamine were coupled giving 14 mg (20%) of the title product. LCMS(an20p15); RT = 7.25 min, (M+1) = 539.1

Example 61

4-Amino-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

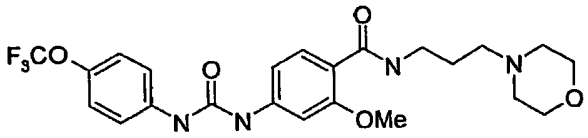


2-methoxy-4-nitro-benzoic acid (3.0 g, 15.5 mmol) was dissolved in THF(180 ml) and the mixture was heated to reflux (70 °C). Carbonyl diimidazol (3.7 g, 22.8 mmol) was added in 3 portions with 20 minutes intervals – with continued refluxing. After the last addition reaction is allowed to reflux for another 1 h. The reaction mixture was cooled to room temperature followed by addition of 3-morpholin-4-yl-propylamine (4.4 g, 30.4 mmol) and the reaction was left overnight. The solvent was removed *in vacuo* and to the crude product was added a mixture of 200 ml EtOAc and 200 ml of water. The organic phase is washed with 2*200 ml water and 1*200 ml of brine. The combined organic phases was dried over $MgSO_4$ and concentrated giving a clear oil. Crystallisation can be obtained by adding diethylether followed by evaporation. The product (7.6 g, 23 mmol) was dissolved in methanol (120 ml) and 10 % Pd/C (40 mg) was added. A pressure of hydrogen atmosphere was applied and the reaction was left over night. Filtration through a plug of celite gave 7.36 g of the title product (94 % over all yield).

^{1}H-NMR (300 MHz, CD_3Cl): δ 1H, 7.79 (s, 1H), 4.03 (s, 2H), 3.90 (s, 3H).

Example 62

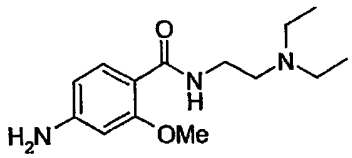
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide



To a solution of 4-Amino-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide (20 mg, 0.068 mmol) (example 61) in dichloromethane (1 mL) was 4-trifluoromethoxyphenyl isocyanate (19 □L , 0.136 mmol) added and the reaction was stirred under inert atmosphere for three days. The solvent was removed *in vacuo.* The crude product was chromatographed (silica, CH_2Cl_2/methanol, 92:8) giving 3.4 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.89 (s, 3H), 8.04 (br t, 1H), 9.09 (s, 1H), 9.12 (s, 1H). LCMS(an10p15): found (M+1) = 497.

Example 63

4-Amino-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide



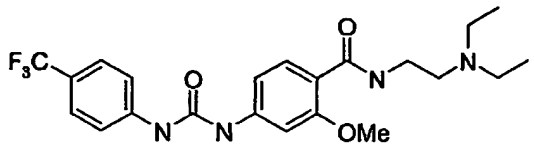
A solution of 2-Methoxy-4-nitrobenzoic acid (1.5 g, 7.6 mmol) in dry dichloromethane (15 mL) was placed on an ice bath whereupon oxalyl chloride (0.6 mL, 6.8 mmol) followed by *N,N*-dimethylformamide (2 μL) were added under inert atmosphere. The mixture was stirred for 30 min at 0 °C followed by 1h in room temperature. Triethylamine (2.1 mL, 15 mmol) and N,N-diethylethylenediamine (1.1 mL, 7.6 mmol) were added and a precipitation was formed. The reaction mixture was stirred for 48h. To the reaction mixture was added EtOAc (60 mL) and the organic layer was washed with Na_2CO_3 (sat.), dried ($MgSO_4$), and concentrated *in vacuo.* The reaction was giving 2.0 g of *N*-(2-diethylamino-ethyl)-2-methoxy-4-nitro-benzamide (99 %). ^{1}H NMR (300 MHz, CD_3Cl): δ 1.06 (t, 6H), 4.07 (s, 3H).

The product (2.0 g, 6.8 mmol) was dissolved in ethanol (20 mL) and 10 % Pd/C (50 mg) was added and thereafter was the flask evacuated and filled with nitrogen. The mixture was stirred in an H_2 atmosphere 48h. The catalyst was filtered off using a pad of celite and the remaining solution was concentrated *in vacuo.* The crude product was

chromatographed (silica, dichloromethane/ethanol/ ammoniak, 100:15:1.5) giving 1.0 g (57%) of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.05 (t, 6H), 2.53-2.65 (m, 6H).

Example 64

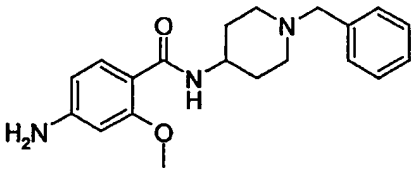
***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**



To a solution of *N*-(2-Diethylamino-ethyl)-2-methoxy-4-amino-benzamide (20 mg, 0.075 mmol) (example 74) in dichloromethane (1 mL) was trifluorophenylisocyanate (28 mg, 0.15 mmol) added and the reaction was stirred under inert atmosphere for four days. A white precipitate had been formed. The solvent was removed *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol/ammoniak, 200:10:1) giving 11 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.05 (t, 6H), 2.56 (q, 4H), 2.65 (t, 2H), 3.54 (q, 2H), 3.94 (s,3H), 6.48 (dd, 1H), 7.56 (q, 4H), 7.83 (d, 1H), 7.92 (d, 1H), 8.74 (t, 1H), 8.91 (s, 1H), 8.93 (s, 1H).

Example 65

4-Amino-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide



The title compound was prepared according to the example described in example 74 giving after the two reaction steps and the purification procedure 0.6 g (33%) of the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.52 (s, 2H), 4.02-4.11 (m, 1H), 3.86 (s, 3H).

A general method for preparing unsymmetrical amines:

Example 66

***N*^{1}-methyl,*N*^{1}-ethyl- ethyldiamine hydro chloride**

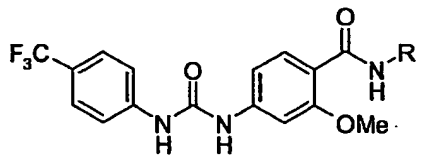
To a suspension of bromoethylphtalimide (8.9 g, 35 mmol) in dry xylene (18 mL) was *N*-ethylmethylamine (6.25 mL, 73 mmol) added and the reaction was stirred over night at 150°C. The reaction was allowed to reach room temperature before it was made basic with 2 M Na_2CO_3-solution (pH = 9). Thereafter was the reaction extracted with EtOAc (3 x

70 mL) and the combined organic phases dried ($MgSO_4$) and evaporated giving a brownish oil. Water (2 mL) and 12 N HCl (12 mL) were added and the solution was heated for 6h at 130°C when a precipitation was formed. The precipitate was filtered off and washed with cold water and the water phase was evaporated giving 4.8 g (78%) of the title product.

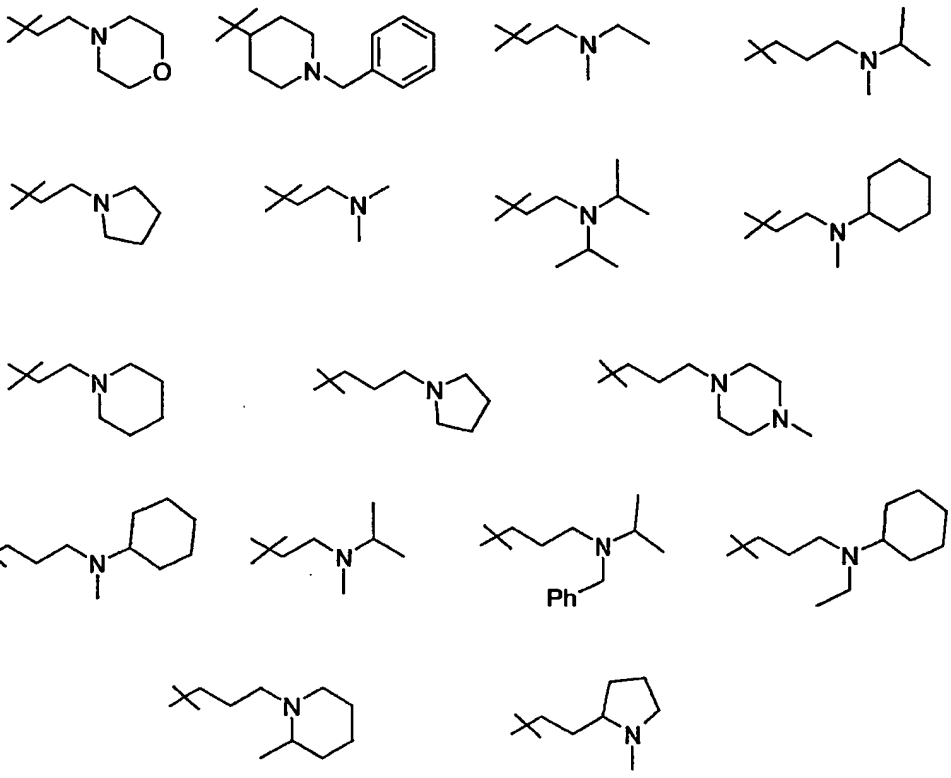
According to the general procedures described hereby, the following compounds were prepared:

Method A: To a solution of Ex. 45 (30 mg, 0.085 mmol) in dichloromethane (0.25 mL) and dimethylformamide (0.25 mL) was HOBT (12 mg, 0.085 mmol) added and the solution was cooled to 0°C whereupon EDAC (16 mg, 0.085 mmol) was added. The reaction was left at 0°C for 20 min before the amine (1-1.5 equiv.) and diisopropylethylamine (1-3 equiv.) were added and the stirring continued at room temperature for one day or more. EtOAc was added to the reaction mixture and the organic phase was washed with $NaHCO_3$ (sat). The aqueous phase was extracted with EtOAc and the combined organic phases was dried ($MgSO_4$) and concentrated giving the crude product.

Method B: To a solution of Ex. 45 (70 mg, 0.20 mmol) in dichloromethane (3.5 mL) and *N,N*-dimethylformamide (0.35 mL) were PS-DDC (0.5 g, 1.27 mmol/g), HOBT (40 mg, 0.29 mmol) and the amine 1 equiv.) added and the mixture was stirred over night. The reaction mixture was filtered off and washed with dichloromethane, and concentrated *in vacuo*. The crude product was purified by acidic ion exchange chromatography (SCX-colon) the product.



R =



Example 67

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method B was the title compound synthesised giving 35 mg (53%) of the product. LCMS (an20p15): RT = 5.72 min, (M+1) = 467.

Example 68

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.49 min, (M+1) = 527. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.48 (s, 2H), 3.93 (s, 3H), 3.93-4.05 (m, 1H), 8.12 (s, 1H), 8.15 (s, 1H).

Example 69

***N*-[2-(Ethyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.49 min, (M+1) = 439. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.08 (t, H), 2.27 (s, 3H), 3.95 (s, 3H), 9.01 (s, 1H), 9.03 (1H).

Example 70

***N*-[3-(Isopropyl-methyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 0.98 (d, 6H), 2.20 (s, 3H), 3.91 (s, 3H), 8.66 (s, 1H), 8.90 (s, 1H).

Example 71

2-Methoxy-*N*-(2-pyrrolidin-1-yl-ethyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method B was the title compound synthesised giving 29 mg (46%) of the product. LCMS (an20p15): RT = 5.79 min, (M+1) = 451.

Example 72

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method B was the title compound synthesised giving 13 mg (23%) of the product. LCMS (an20p15): RT = 5.66 min, (M+1) = 425.

Example 73

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method B was the title compound synthesised giving 18 mg (27%) of the product. LCMS (an20p15): RT = 6.32 min, (M+1) = 481.0 m/z.

Example 74

***N*-[2-(Cyclohexyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.65 min, (M+1) = 493. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.63 (d, 1H), 2.31 (s, 3H), 3.91 (s, 3H), 9.08 (s, 2H).

Example 75

2-Methoxy-*N*-(2-piperidin-1-yl-ethyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method B was the title compound synthesised giving 14 mg (22%) of the product. LCMS (an20p15): RT = 5.99 min, (M+1) = 465.

Example 76

2-Methoxy-*N*-(3-pyrrolidin-1-yl-propyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 5.93 min, (M+1) = 465. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.90 (s, 3H), 9.08 (s, 1H), 9.14 (s, 1H).

Example 77

2-Methoxy-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 5.05 min, (M+1) = 494. ^{1}H NMR (300 MHz, CD_3Cl): δ 2.28 (s, 3H), 3.94 (s, 3H), 9.03 (s, 1H), 9.07 (s, 1H).

Example 78

***N*-[3-(Cyclohexyl-methyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.61 (d, 1H), 2.26 (s, 3H), 3.90 (s, 3H), 9.07 (s, 1H), 9.13 (s, 1H).

Example 79

***N*-[2-(Isopropyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.12 min, (M+1) = 453. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.05 (d, 6H), 2.27 (s, 3H), 2.89-2.98 (m, 1H), 3.92 (s, H), 9.07 (s, 1H).

Example 80

***N*-[3-(Benzyl-isopropyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.27 min, (M+1) = 543. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.01 (d, 6H), 3.55 (s, 2H), 3.82 (s, 3H), 9.09 (s, 1H), 9.15 (s, 1H).

Example 81

***N*-[3-(Cyclohexyl-ethyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.13 min, (M+1) = 521. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.00 (t, 3H), 1.61 (d, 1H), 3.89 (s, 3H), 9.10 (s, 1H), 9.16 (s, 1H).

Example 82

2-Methoxy-*N*-[3-(2-methyl-piperidin-1-yl)-propyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.26 min, (M+1) = 493. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.03 (d, 3H), 3.92 (s, 3H), 9.03 (s, 1H), 9.09 (s, 1H).

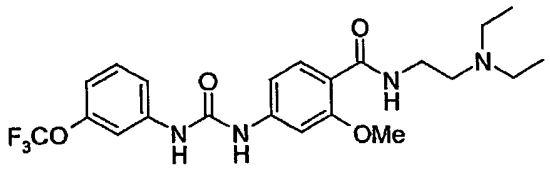
Example 83

2-Methoxy-*N*-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 5.76 min, (M+1) = 465. ^{1}H NMR (300 MHz, CD_3Cl): δ 2.30 (s, 3H), 3.94 (s, 3H), 9.00 (s, 1H), 9.02 (s, 1H).

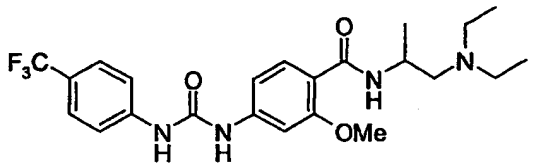
Example 84

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide**



Example 85

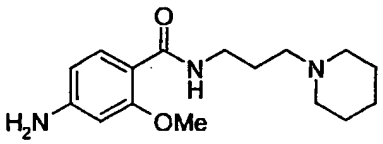
***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**



To a solution of 4-amino-*N*-(2-diethylamino-1-methyl-ethyl)-2-methoxy-benzamide (56 mg, 0.2 mmol) (synthesised using the same method as for example 74) in dry dichloromethane (5mL) was 4-trifluorotosyl isocyanate (35 □L, 0.25 mmol) added and the reaction was stirred under inert atmosphere for four days. The solvent was removed *in vacuo*. The crude product was chromatographed (Al_2O_3, CH_2Cl_2/methanol/ammoniak, 10:0.25+0.5%) giving 27 mg of the title product (29 %).

Example 86

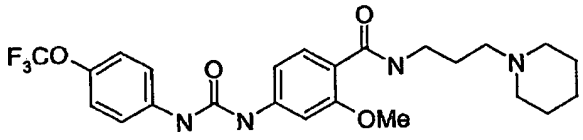
4-Amino-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide



To a refluxing solution of 2-methoxy-4-nitro-benzoic acid (5.6 g, 29 mmol) in dry THF (mL) was carbonyldiimidazol (3 x 2.3 g, 42 mmol) added in three portions with 15 min in between. After 20 minutes continuous refluxing the reaction was cooled to room temperature and 3-amino-propyl-piperidine (4.5 g, 32 mmol) was added. The reaction mixture was left stirring over night. Water and EtOAc was added and the organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol/ammoniak, 9:1 + 1%) giving 6.8 g of 2-methoxy-4-nitro-N-(3-piperidin-1-yl-propyl) benzamide (74 %). The product was dissolved in ethanol (250 mL) and 10 % Pd/C (200 mg) was added under a nitrogen flow. A balloon containing H_2 was collected to the flask and the reaction mixture was stirred for 2h. The catalyst was filtered off using a pad of celite and the remaining solution was concentrated *in vacuo* giving 4.9 g (80 %) of the title product.

Example 87

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

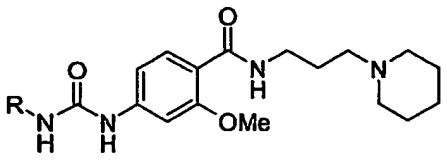


To a solution of example 97 (58 mg, 0.2 mmol) in dichloromethane was 4-trifluoromethoxyphenyl isocyanate (35 μL, 0.25 mmol) added and the reaction was stirred over night in inert atmosphere. The solvent was removed *in vacuo*. The crude product was chromatographed (Al_2O_3, CH_2Cl_2/methanol/ammoniak, 10:0.25+0.5%) giving 20 mg of the title product (20 %).

According to the procedure described in example 98 (from anilines and isocyanates) or according to the general method described below (from anilines and carboxylic acid) were the following compounds prepared:

General method for preparing ureas from anilines and carboxylic acids:

To a solution of the carboxylic acid (0.25 mmol) in dry toluene (5 mL) under inert atmosphere were diphenylphosphoryl azide (54 μL, 0.25 mmol) and triethylamine (35 μL, 0.25 mmol) and the reaction mixture was heated to reflux for 1h. 4-Amino-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide, Example 97 (44 mg, 0.15 mmol) dissolved in hot toluene (2 mL) was added and the reaction mixture was left over night in room temperature. The solvent was removed *in vacuo*. The crude product was usually purified through chromatography (silica, CH_2Cl_2/methanol/ammoniak, 10:0.25 + 0.5 %) giving the desired product.



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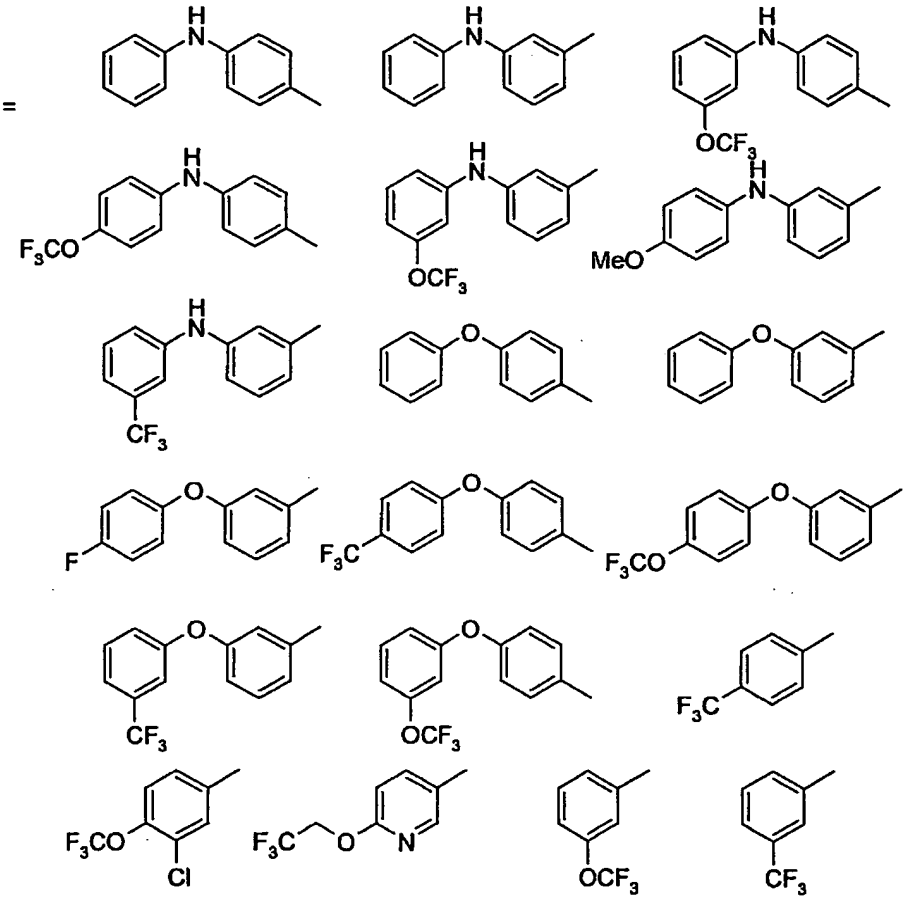


Example 88

2-Methoxy-4-[3-(4-phenylamino-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide)

Ex 86 and 4-Phenylamino-benzoic acid were coupled giving 41 mg (54%) of the title product. LCMS (an20p15): RT = 6.05 min, (M+1) =502.

Example 89

2-Methoxy-4-[3-(3-phenylamino-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 86 and 3-Phenylamino-benzoic acid were coupled giving 53 mg (71%) of the title product. LCMS (an20p15): RT = 5.44 min, (M+1) =502.

Example 90

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(3-trifluoromethoxy-phenylamino)-phenyl]-ureido}-benzamide

Ex 86 and 4-(3-trifluoromethoxy-phenylamino)-benzoic acid were coupled giving 46 mg (52%) of the title product. LCMS (an20p15): RT = 6.83 min, (M+1) = 586.

Example 91

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(4-trifluoromethoxy-phenylamino)-phenyl]-ureido}-benzamide

Ex 86 and 4-(4-trifluoromethoxy-phenylamino)-benzoic acid were coupled giving 67 mg (76%) of the title product. LCMS (an20p15): RT = 6.89 min, (M+1) = 586.

Example 92

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[3-(3-trifluoromethoxy-phenylamino)-phenyl]-ureido}-benzamide

Ex 86 and 3-(3-Trifluoromethoxy-phenylamino)-benzoic acid were coupled giving 50 mg (60%) of the title product. LCMS (an20p15): RT = 6.24 min, (M+1) = 586.

Example 93

2-Methoxy-4-{3-[3-(4-methoxy-phenylamino)-phenyl]-ureido}-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 86 and 4-(4-Methoxy-phenylamino)-benzoic acid were coupled giving 20 mg (25%) of the title product. LCMS (an20p10): RT = 5.77 min, (M+1) = 532.

Example 94

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[3-(4-trifluoromethyl-phenylamino)-phenyl]-ureido}-benzamide

Ex 86 and 3-(3-Trifluoromethyl-phenylamino)-benzoic acid were coupled giving 30 mg (35%) of the title product. LCMS (an20p10): RT = 6.19 min, (M+1) = 570.

Example 95

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 86 and 4-phenoxy-phenyl isocyanate were coupled giving 22.6 mg (23 %) of the title product. LCMS (an20p10): RT = 5.84 min, (M+1) = 503.

Example 96

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 86 and 3-phenoxyphenyl isocyanate were coupled giving 69 mg (68%) of the title product. LCMS (an20p15): RT = 6.55 min, (M+1) = 503.

Example 97

4-{3-[3-(4-Fluoro-phenoxy)-phenyl]-ureido}-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 86 and 4-(4'-fluorophenoxy)benzoic acid were coupled giving the title product. LCMS (an20p10): RT = 6.06 min, (M+1) = 521.

Example 98

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(4-trifluoromethyl-phenoxy)-phenyl]-ureido}-benzamide

Ex 86 (86 mg, 0.30 mmol) and 4-(4'-trifluoromethylphenoxy)benzoic acid (160 mg, 0.57 mmol) were coupled giving 47 mg (27%) of the title product. LCMS (an20p15): RT = 6.84 min, (M+1) = 571. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.86 (t, 2H), 3.90 (s, 3H), 6.70 (d, 1H), 8.21 (t, 1H), 9.13 (s, 1H), 9.33 (s, 1H).

Example 99

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(4-trifluoromethoxy-phenoxy)-phenyl]-ureido}-benzamide

Ex 86 and 4-(4-trifluoromethoxy-phenoxy)-benzoic acid were coupled giving 62 mg (71%) of the title product. LCMS (an20p15): RT = 7.17 min, (M+1) = 587.

Example 100

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[3-(3-trifluoromethyl-phenoxy)-phenyl]-ureido}-benzamide

Ex 86 and 3-(3-trifluoromethyl-phenoxy)-benzoic acid were coupled giving 24 mg (28%) of the title product. LCMS (an20p10): RT = 6.41 min, (M+1) = 571.

Example 101

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(3-trifluoromethoxy-phenoxy)-phenyl]-ureido}-benzamide

Ex 86 and 4-(3-Methoxy-phenoxy)-benzoic acid were coupled giving 10 mg (11%) of the title product. LCMS (an20p15): RT = 7.25 min, (M+1) = 587.

Example 102

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

Ex 86 and 4-trifluoromethylphenyl isocyanate were coupled giving 15.5 mg (16 %) of the title product. LCMS (an20p15): RT = 6.16 min, (M+1) = 479.

Example 103

4-[3-(3-Chloro-4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 86 (0.14 g, 0.47 mmol) and 3-chloro-4-trifluoromethoxybenzoic acid (0.20 g, 0.83 mmol) were coupled giving 38 mg (%) of the title product. LCMS (an20p15): RT = 6.54 min, (M+1) =529.

Example 104

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-ureido}-benzamide

Ex 86 and 6-(2,2,2-Trifluoro-ethoxy)-nicotinic acid were coupled giving 15 mg (20%) of the title product. LCMS (an20p15): RT = 5.83 min, (M+1) = 510.

Example 105

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 86 and 3-trifluoromethoxybenzoic acid were coupled giving 13.3 mg (18 %) of the title product. LCMS (an20p15): RT = 7.55 min, (M+1) = 495.

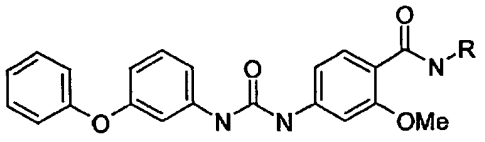
Example 106

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(3-trifluoromethyl-phenyl)-ureido]-benzamide

Ex 86 and 3-trifluorotosyl isocyanate were coupled giving 36.7 mg (38%) of the title product. LCMS (an20p15): RT = 6.19 min, (M+1) = 479.

According to the procedure described hereby the following compounds were prepared:
General procedure:

2-(3,5-Dimethoxy-4-formyl-phenoxy)ethyl polystyrene resin (200 mg, loading indicated by supplier 0.78 mmol/g, 0.16 mmol) was placed in a 12 mL fritted Teflon reactor fixed on an orbital shaker. A solution of amine (0.48 mmol, 3 eq) in NMP (1 mL), a solution of $NaCNBH_3$ (30 mg, 3 eq) in NMP (1 mL), AcOH (100 μL), and water (10 μL) was added to the resin. The mixture was shaken at room temperature over night. The resin was washed according to the general washing procedure described below. General washing procedure: NMP (2 mL), DCM (2 mL), MeOH (2 mL), DCM (2 mL), and NMP (2 mL). A solution of 2-methoxy-4-nitrobenzoic acid (99 mg, 3 eq) and 1-hydroxybenzotriazole (68 mg, 3 eq) in NMP/DCM (1 mL/1 mL) was added. Diisopropylcarbodiimide (80 μL, 3 eq) and diisopropylethylamine (30 μL, 1 eq) was added. The mixture was shaken at room temperature for 4 h, and hereafter the resin was washed according to the standard procedure. A solution of $SnCl_2 \cdot H_2O$ (180 mg, 5 eq) in NMP (2 mL) was added and diisopropylethylamine (30 μL, 1 eq) was added. The mixture was shaken over night at room temperature, and hereafter the resin was washed with NMP (2 mL), DCM (2 mL), MeOH (2 mL), 2×DCM (2 mL). The resin was treated with a solution of 3-phenoxyphenyl isocyanate (65 μL, 3 eq) in dry DCM (2 mL) and shaken at room temperature for 3 h. The resin was washed with NMP (2 mL), DCM (2 mL), MeOH (2 mL), 2× DCM (2 mL), and the treatment with 3-phenoxyphenyl isocyanate (65 μL, 3 eq) in dry DCM (2 mL) was repeated. Finally the resin was washed with NMP (2 mL), 5% diisopropylamine in NMP (2 mL), NMP (2 mL), DCM (2 mL), 5% AcOH in DCM (2 mL), DCM (2 mL), MeOH (2 mL), 3×DCM (2 mL). The resin was treated with TFA/DCM/TES (60:35:5, v/v, 2 mL) for 2 h at room temperature and hereafter washed with DCM (1 mL) to cleave the product from the resin. The samples were evaporated, redissolved in water/acetonitrile (2:8, v/v, 1 mL) and purified by preparative LC-MS. The compounds were eluted over 20 min with 20-95% acetonitrile in water (both solvents contained 0.01% TFA or 0.01% formic acid).



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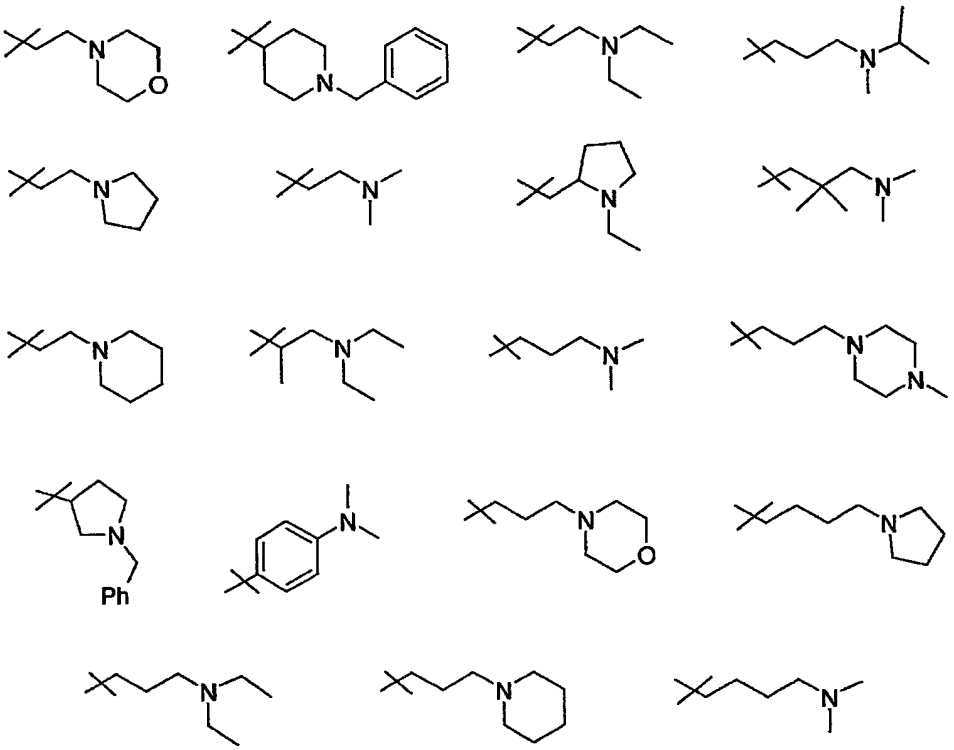


Example 107

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide

From the reaction was 91 mg of the crude product isolated giving after purification 13 mg (13%)of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.98 (s, 1H, NH^+), 8.49 (s, 1H), 8.23 (s, 1H), 8.08 (s, 1H), 7.72 (d, 1 H, J = 7.7 Hz), 7.26-6.59 (m, 11 H), 3.91 (d, 2H, J = 12 Hz), 3.72 (s, 3H, OCH_3), 3.68 (s, 4H), 3.54 (d, 2H, J = 12 Hz), 3.23 (s, 2H), 2.88 (br t, 2H). LCMS(an10p15): RT = 8.39 min, (M+1) = 491.

Example 108

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 161 mg of the crude product isolated giving after purification 37 mg (34%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H, NH^+), 8.41 (s, 1H), 8.20 (s, 1H), 7.83 (d, 1H, J = 6.8 Hz), 7.66 (d, 1 H, J = 7.7 Hz), 7.32-6.52 (m, 16 H), 3.97 (s, 3H), 3.67 (s, 3H, OCH_3), 3.35 (s, 2H), 2.64 (s, 2H), 2.01 (s, 2H), 1.81 (br s, 2H).
LCMS(an10p15): RT = 9.05 min, (M+1) = 551.

Example 109

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 97 mg of the crude product isolated giving after purification 6.6 mg (9%)of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.43 (s, 1H), 9.20 (s, 1H), 8.45 (m, 2H), 7.78 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.39-6.39 (m, 9H), 3.84 (s, 3H, OCH_3), 3.78 (br s, 2H), 3.21 (m, 2H), 3.14 (m, 4H), 1.32 (t, J = 7.4 Hz, 6H). LCMS(an10p15): RT = 5.79 min, (M+1) = 477, RT = 7.19 min, (M+1) = 186, 20% (aniline from isocyanate)

Example 110

***N*-[3-(Isopropyl-methyl-amino)-propyl]-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

To a solution of 2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzoic acid (80 mg, 0.2 mmol), prepared using the same procedure as in example 45, in dichloromethane (20 mL) were HOBT (38 mg, 0.27 mmol), EDAC (61 mg, 0.32 mmol), N^1-isopropyl-N^1-methyl-propyldiamine hydrochloride (52 mg, 0.25 mmol) and diisopropylethylamine (66 mg, 88 μL, 0.5 mmol) added and the stirring continued at room temperature over night. EtOAc was added to the reaction mixture and the organic phase was washed with NaHCO3 (sat). The aqueous phase was extracted with EtOAc and the combined organic phases was dried ($MgSO_4$) and concentrated giving the crude product. The crude product was chromatographed (silica, CH_2Cl_2/methanol, 85:15) followed by a SCX-colon and preparative LCMS giving 2.2 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.85 (s, 3H), 8.19 (t, 1H), 9.34 (s, 1H), 9.59 (s, 1H). LCMS (an20p15): (M+1) = 491.

Example 111

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide

From the reaction was 111 mg of the crude product isolated giving after purification 18 mg (20%)of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.71 (s, 1H), 8.74 (s, 1H), 8.49 (s, 1H), 8.29 (s, 1H), 7.65 (s, 1 H), 7.34-6.95 (m, 11 H), 3.65 (s, 3H), 3.62 (s, 4H), 3.18 (s, 2H), 2.75 (s, 2H), 1.92 (s, 4H). LCMS(an10p15): RT = 8.51 min , (M+1) = 475.

Example 112

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 113 mg of the crude product isolated giving after purification 21 mg (23%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.68 (s, 1H, NH^+), 8.70 (s, 1H), 8.42 (br s, 1H), 8.31 (s, 1H), 7.67 (d, 1 H, J = 7.5 Hz), 7.31-6.52 (m, 11 H), 3.69 (s, 3H, OCH_3), 3.59 (s, 2H), 3.31 (s, 2H), 2.76 (s, 6H). LC-MS(an20p15): RT = 8.30 min, (M+1) = 449.

Example 113

***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 124 mg of the crude product isolated giving after purification 10 mg (13%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.43 (s, 1H), 9.20 (s, 1H), 8.60 (t, 1H), 7.77 (d, J = 8.7 Hz, 1 H), 7.47 (s, 1H), 7.35-6.85 (m, 9 H), 6.59 (d, 1H), 3.83 (s, 3H, OCH_3), 3.59 (m, 4H), 3.21 (m, 1H), 2.81 (m, 2H), 2.13 (m, 1H), 1.96 (m, 2H), 1.82 (m, 1H), 1.26 (t, , J = 7.2 Hz, 3H). LCMS(an10p15): RT = 5.90 min, (M+1) = 489.

Example 114

***N*-(3-Dimethylamino-2,2-dimethyl-propyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

To a solution of 4-amino-*N*-(3-dimethylamino-2,2-dimethyl-propyl)-2-methoxy-benzamide (25 mg, 0.09 mmol), prepared according to the procedure for example 97, in dichloromethane (3 mL) was 3-phenoxyphenyl isocyanate (37 mg, 32 μL, 0.18 mmol) added and the reaction was stirred under inert atmosphere over night. The solvent was removed *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol, 92:8) giving 37 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.92 (s, 3H), 8.82 (t, 1H), 8.74 (s, 1H), 8.94 (s, 1H).

Example 115

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(2-piperidin-1-yl-ethyl)-benzamide

From the reaction was 90 mg of the crude product isolated giving after purification 18 mg (18 %) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.72 (s, 1H, NH^+), 9.09 (s, 1H), 8.80 (s, 1H), 8.33 (s, 1H), 7.67 (s, 1 H), 7.27-6.76 (m, 10 H), 6.52 (d, 1H, J = 7.2 Hz), 3.69 (s, 3H, OCH_3), 3.58 (s, 2H), 3.41 (s, 2H), 3.04 (s, 2H), 2.58 (s, 2H), 1.73 (s, 4H), 1.27 (s, 2H). LCMS(an10p15): RT = 8.76 min, (M+1) = 489.

Example 116

***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 118 mg of the crude product isolated giving after purification 17 mg (17%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.18 (s, 1H, NH^+), 9.04 (s, 1H), 8.72 (s, 1H), 8.27 (s, 1H), 7.69 (br d, 1 H), 7.32-6.50 (m, 11 H), 3.74 (s, 3H, OCH_3), 3.36 (s, 2H), 2.99 (br s, 4H), 2.90 (s, 3H), 1.88 (s, 1H), 1.16 (t, 6H, J = 7.1H Hz). LCMS(an10p15): RT = 8.65 min, (M+1) = 491.

Example 117

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 117 mg of the crude product isolated giving after purification 15 mg (16 %) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.86 (s, 1H, NH^+), 8.99 (s, 1H), 8.69 (s, 1H), 8.16 (s, 1H), 7.65 (d, 1 H, J = 7.5 Hz), 7.31-6.54 (m, 11 H), 3.73 (s, 3H, OCH_3), 3.35 (s, 2H), 2.91 (s, 2H), 2.67 (s, 6H), 1.88 (s, 2H). LCMS(an10p15): RT = 8.31 min, (M+1) = 463.

Example 118

2-Methoxy-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide

From the reaction was 113 mg of the crude product isolated giving after purification 8.0 mg (7 %) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.92 (s, 1H), 9.84 (s, 1H,), 8.81 (t, 1H, J = 5.7 Hz, N*H*CO), 8.40 (d, 1H, J = 8.5 Hz), 8.08-7.61 (m, 11H, m), 7.27 (d, 1H, J = 7.5 Hz), 4.51 (s, 6H, OCH_3 + CH_3), 3.97 (br m, 6H), 3.63 (s, 2H), 3.43 (s, 4H), 3.31 (s, 2H). LCMS(an10p15): RT = 7.56 min, (M+1) = 518.

Example 119

***N*-(1-Benzyl-pyrrolidin-3-yl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 167 mg of the crude product isolated giving after purification 23 mg (22%) of the title product.^{1}H-NMR ($CDCl_3$): δ 11.61 (s, 1H, NH^+), 8.81 (s, 1H), 8.57 (s, 1H), 8.34 (s, 1H), 7.62 (br d, 1 H), 7.25-6.49 (m, 16 H), 4.55 (s, 1H), 4.05 (s, 3H, OCH_3), 3.06 (d, 4H), 3.36 (s, 1H), 3.13 (s, 1H), 2.79 (s, 1H), 2.37 (s, 1H). LCMS(an10p15): RT = 9.30 min, (M+1) = 537.

Example 120

***N*-(4-Dimethylamino-phenyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 122 mg of the crude product isolated giving after purification 25 mg (25%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.14 (s, 1H, NH^+), 8.53 (s, 1H), 8.21 (s, 1H), 7.73 (d, 1H, H = 9.0 Hz), 7.51 (d, 1 H, J = 8.7 Hz), 7.36-6.54 (m, 15 H), 3.79 (s, 3H, OCH_3), 3.03 (s, 6H). LCMS(an10p15): RT = 8.83 min, M+1 = 497.

Example 121

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide

The title product was prepared according to the procedure described in **Ex 62**, giving after purification an isolated yield of 16.7 mg. ^{1}H-NMR (dmso-d_6): δ 3.89 (s, 3H), 8.04 (s, 1H), 9.09 (s, 1H), 9.12 (s, 1H). LCMS(an10p15): (M+1) = 497.

Example 122

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(4-pyrrolidin-1-yl-butyl)-benzamide

From the reaction was 93 mg of the crude product isolated giving after purification 18 mg (20%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.33 (s, 1H), 9.13 (s, 1H), 8.65 (s, 1H), 7.94 (t, J = 5.9 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1 H), 7.57 (s, 1H), 7.34-6.61 (m, 9H), 3.86 (s, 3H, OCH_3), 3.36 (m, 2H), 3.13 (br s, 4H), 2.99 (m, 2H), 1.98 (br s, 4H), 1.73 (m, 2H), 1.56 (m, 2H). LCMS(an20p10): RT = 5.76 min, (M+1) = 503.

Example 123

***N*-(3-Diethylamino-propyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 94 mg of the crude product isolated giving after purification 18 mg (20%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.65 (s, 1H), 9.39 (s, 1H), 8.21 (t, 1H), 7.81 (d, 1 H), 7.50 (s, 1H), 7.22-6.85 (m, 9 H), 6.58 (d, 1H), 3.83 (s, 3H, OCH_3), 3.45 (br q, 2H), 3.05-2.91 (br m, 6H), 1.95 (br t, 2H), 1.23 (t, 6H, J = 7.2 Hz). LCMS(an10p15): RT = 8.62 min, (M+1) = 491.

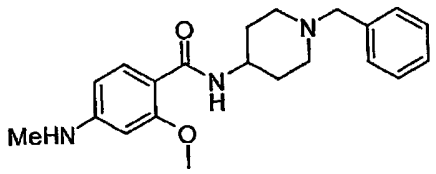
Example 124

***N*-(4-Dimethylamino-butyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 99 mg of the crude product isolated giving after purification 8.4 mg (20%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.13 (s, 1H), 8.88 (s, 1H), 7.98 (t, J = 5.7 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1 H), 7.28 (s, 1H), 7.32-6.60 (m, 10 H), 3.83 (s, 3H, OCH_3), 3.35 (m, 2H), 2.93 (m, 2H), 2.66 (s, 6H), 2.02 (m, 2H), 1.56 (m, 2H). LCMS(an20p10): RT = 5.57 min, (M+1) = 477.

Example 125

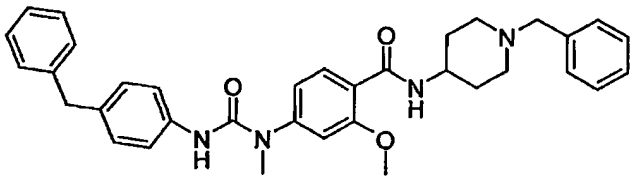
***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-methylamino-benzamide**



4-Amino-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide (synthesised according to the same procedure as example 97) was dissolved in methanol and sodium methoxide (5.7 equiv.) and paraformaldehyde (1.5 equiv.) were added. The reaction was stirred over night under inert atmosphere at 40 °C. The mixture was cooled to room temperature whereupon sodium borohydride (2.4 equiv.) was added slowly and the reaction was continuously stirred over night at 50 °C. The solvent was removed *in vacuo*. The residue was dissolved in NaHCO3-solution (150 mL), extracted with *tert*-butylmethylether (3 x 100 mL). The combined organic phases was dried (Na2SO4) and concentrated. The crude product was chromatographed (silica, dichloromethane/methanol/ ammonia, 100:10:1) giving the title product (78%). ^{1}H NMR (300 MHz, CD_3Cl): δ 2.89 (d, 3H, -NHMe).

Example 126

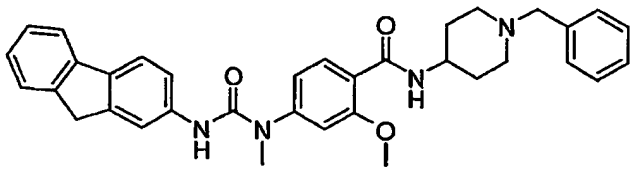
4-[3-(4-Benzyl-phenyl)-1-methyl-ureido]-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide



To a solution Ex 140 (20 mg, 0.057 mmol) in dichloromethane (0.5 mL) was 4-benzylphenyl isocyanate (24 mg, 0.11 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-trisamine (3.56 mmol/g, 100 mg) was added. After two days was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 28 mg (87%) of the title product. LCMS (an20p15): RT = 6.75 min, (M+1) = 563.

Example 127

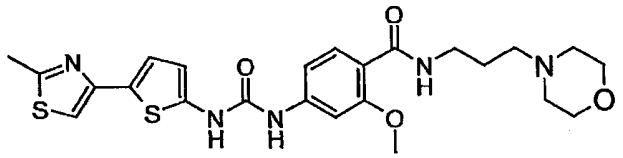
***N*-(1-Benzyl-piperidin-4-yl)-4-[3-(9H-fluoren-2-yl)-1-methyl-ureido]-2-methoxy-benzamide**



To a solution **Ex 125** (20 mg, 0.057 mmol) in dichloromethane (0.5 mL) was 9H-fluoren-2-yl isocyanate (24 mg, 0.11 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-trisamine (3.56 mmol/g, 100 mg) was added. After two days was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 27 mg (85%) of the title product. LCMS (an20p15): RT = 6.62 min, (M+1) = 561.

Example 128

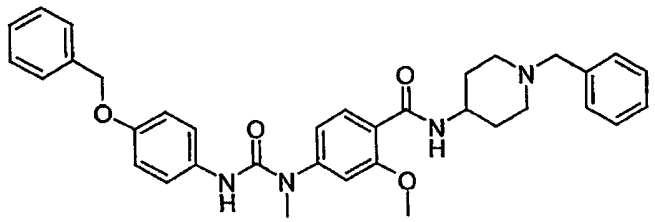
2-Methoxy-4-{3-[5-(2-methyl-thiazol-4-yl)-thiophen-2-yl]-ureido}-*N*-(3-morpholin-4-yl-propyl)-benzamide



To a solution of 5-(2-methyl-1,3-thiazol-4-yl)thiophen-2-caboxylic acid (102 mg, 0.45 mmol) in toluene (5 mL) were dihenylphosphorylazid (79 μL, 0.37 mmol) and triethylamine (42 □L) added and therafter was the reaction mixture heated to reflux. After 3h was **Ex. 61** (67 mg, 0.23 mmol) dissolved in hot toluene (2 mL) added. The reaction was allowed cooled a bit before dichloromethane (2 mL) was added and thereafter was the reaction left over night. The solvent was removed in vacuo. The crude product was purified with acidic ion exchange chromatography (SCX-colon) followed by one more chromatography (silica, dichloromethane/methanol/ammoniak, 9:1+1%) giving 71 mg (61%) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 2.53 (s, 3H), 3.82 (s, 3H), 6.98 (dd, 1H), 8.07 (t, 1H), 9.08 (s, 1H), 9.83 (s, 1H).

Example 129

4-[3-(4-Benzyloxy-phenyl)-1-methyl-ureido]-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide

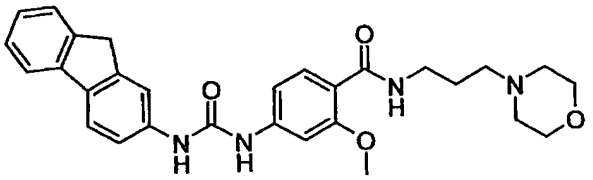


To a solution **Ex 125** (20 mg, 0.057 mmol) in dichloromethane (0.5 mL) was 4-benzyloxy-phenyl isocyanate (24 mg, 0.11 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-trisamine (3.56 mmol/g, 100 mg) was

added. After two days was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 28 mg (85%) of the title product. LCMS (an20p15): RT = 5.73 min, (M+1) = 579.

Example 130

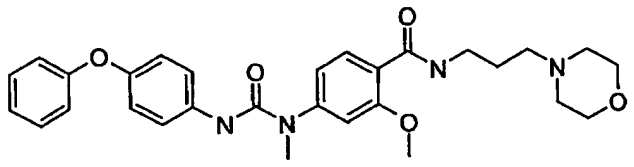
4-[3-(9H-Fluoren-2-yl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide)



To a solution **Ex 61** (20 mg, 0.068 mmol) in dichloromethane (0.5 mL) was 9H-fluoren-2-yl isocyanate (28 mg, 0.14 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-tosyl chloride (1.0 equiv.) was added. After 12h was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with chromatography (dichloromethane/methanol, 92:8) giving 8.5 mg (25%) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 3.40 (s, 3H), 8.05 (t, 1H), 8.87 (s, 1H), 9.02 (s, 1H). LCMS (an20p15): (M+1) = 501 m/z.

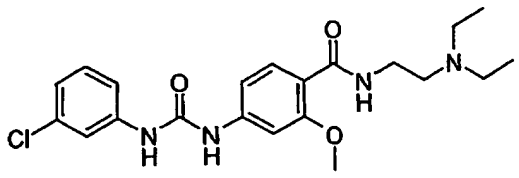
Example 131

2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide



Example 132

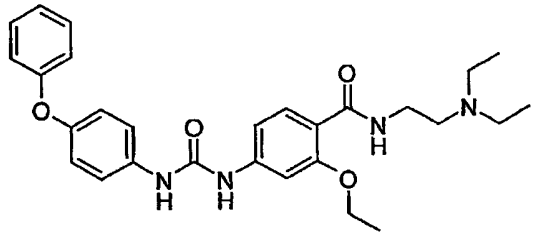
4-[3-(3-Chloro-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide



To a solution of 4-amino-N-(2-diethylamino-ethyl)-2-methoxy-benzamide (30 mg, 0.11 mmol) in dry dichloromethane (1.5 mL) was 3-chlorophenyl isocyanate (28 μL, 0.22 mmol) added and the reaction was stirred three days under inert atmosphere. PS-Trisamine (100 mg, 3.58 mmol/g) was added and after gentle stirring for 2 h, and addition of methanol (2 mL), was the resin removed by filtration. The resin was washed with dichloromethane (2 mL). The solvents were removed *in vacuo* and the crude product was purified through chromatography (silica, CH_2Cl_2/methanol/ammoniak, 101:10: 1) giving the desired product. ^{1}H-NMR (dmso-d_6): δ 0.99 (t, 4H), 2.20 (s, 2H), 3.90 (s, 3H), 8.98 (s, 1H), 9.07 (s, 1H). Mass analysis; found (M+1) = 419.

Example 133

***N*-(2-Diethylamino-ethyl)-2-ethoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



A solution of methyl-4-acetamido-2-ethoxybenzoate (1g, 4.2 mmol) and lithium hydroxide (0.5 g, 21 mmol) in a THF/water mixture (50ml/25ml) was heated to 70°C for 18h. After cooling, solvent was removed *in vacuo* to give a white semi-solid (0.788g, 4.2 mmol, 100%). ^{1}H NMR (300 MHz, D_2O): δ 1.2 (t, 3H), 3.95 (q, 2H), 6.25 (d, 1H), 6.35 (s, 1H), 7.2 (d, 1H).

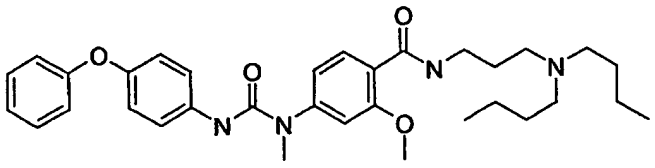
To a cooled (0°C) solution of 4-amino-2-ethoxybenzoic acid, lithium salt (0.78g, 4.17 mmol) in a dioxane/water mixture (50ml/25ml) was added BOC_2O (0.92g, 4.17 mmol). After stirring for 10 minutes at 0°C, the reaction mixture was stirred at RT for 4h. The mixture was then cooled to 0°C and further BOC_2O (1.84g, 8.34 mmol) was added. After stirring for an additional 10 minutes at 0°C, the reaction mixture was stirred at RT for 2 days. Dioxane was removed *in vacuo*. The aqueous phase was diluted with water and washed with dichloromethane (3x). The aqueous phase was then saturated with NaCl, acidified with a 1N aq. HCl solution and quickly extracted with dichloromethane (3x). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid as 4-Amino-2-ethoxy-benzoic acid (0.84 g, 2.96 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H), 1.55 (t, 3H), 4.35 (q, 2H), 6.69 (d, 1H), 6.75 (bs, 1H), 7.76 (s, 1H), 8.06 (d, 1H), 10.8 (bs, 1H)

To a solution of 4-Amino-2-ethoxy-benzoic acid (0.1g, 0.35 mmol) in dichloromethane (20 ml) were added EDAC (0102 g, 0.53 mmol) and HOBt (0.062 g, 0.46 mmol). After stirring for 5 minutes, *N,N*-diethyl-ethylene diamine (60 µl, 0.43 mmol) was added and the reaction mixture was stirred at RT overnight. The mixture was washed with sat. aq. $NaHCO_3$ (3x), brine (2x), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil (0.135 g, 0.35 mmol, 100%). The oil was stirred overnight at RT in a TFA/dichloromethane mixture (3 ml/3 ml). Solvent was removed *in vacuo*. The residue was diluted with water and washed with dichloromethane (3x). The aqueous phase was saturated with NaCl and solid K_2CO_3 was added up to pH = 12. The aqueous phase was extracted with dichloromethane (3x), the organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a pale-brown oil as 4-Amino-*N*-(2-diethylamino-ethyl)-2-ethoxy-benzamide (0.086 g, 0.31 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.04 (bt, 6H), 1.5 (t, 3H), 2.62 (bm,6H), 3.5 (bm, 2H), 3.92 (bs, 2H), 4.12 (q, 2H), 6.18 (s,1H), 6.32 (d, 1H), 8.03 (d, 1H), 8.2 (bs, 1H)

A solution of 4-Amino-*N*-(2-diethylamino-ethyl)-2-ethoxy-benzamide (0.08g, 0.286 mmol) and 4-phenoxyphenyl isocyanate (77.6 µl, 0.429 mmol) in dichloromethane (5 ml) was stirred at RT overnight under an argon atmosphere. PS-trisamine (0.286 mmol) was added and the reaction mixture was stirred for a further 18h00. Methanol (1 ml) was added to dissolve the precipitate. The resin was filtered off and the filtrate was concentrated to give a semi-solid which was triturated with methanol. The solid was filtered, washed with methanol and dried *in vacuo* to give a white powder (0.08 g, 0.163 mmol, 57%). ^{1}H NMR (300 MHz, DMSO): δ 0.97 (t, 6H), 1.45 (t, 3H), 2.53 (m, 6H), 3.35 (q, 2H), 4.18 (q, 2H), 6.95-7.5 (m, 11H), 7.85 (d, 1H), 8.2 (bm, 1H), 8.76 (s, 1H), 8.94 (s, 1H)

Example 134

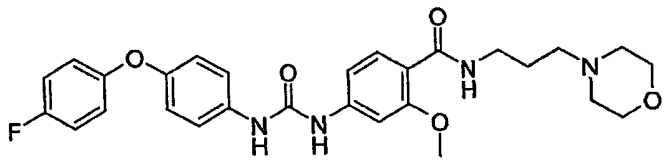
***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide**



^{1}H-NMR ($CDCl_3$): δ 0.90 (m, 6H), 1.33 (m, 8H), 1.80 (m, 2H), 2.47 (m, 6H), 3.37 (s, 3H), 3.53 (q, 2H), 3.98 (s, 3H), 6.40 (s, 1H), 6.95 – 7.06 (m, 7H), 7.32 (m, 4H), 7.98 (bs, 1H), 8.23 (d, 1H)

Example 135

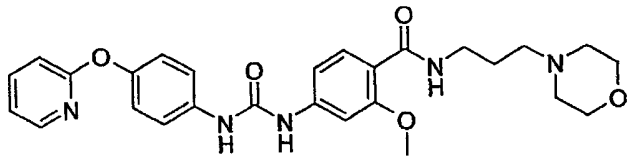
4-{3-[4-(4-Fluoro-phenoxy)-phenyl]-ureido}-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide



^{1}H-NMR ($CDCl_3$): δ 1.80(m 2H), 2.42(m 6H), 3,51(m 2H), 3.66(m 4H), 3.93(s 3H), 6.45(m 1H), 6.91-7.04(m 6H), 7.28(s 1H), 7.39(m 1H), 7.90(m 2H), 8.20(m 1H), 8.48(s 1H), 8.77(s 1H).

Example 136

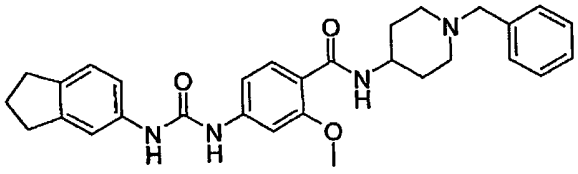
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-{3-[4-(pyridin-2-yloxy)-phenyl]-ureido}-benzamide



^{1}H-NMR ($CDCl_3$): δ 1.82 (m, 2H), 2.41 (m, 6H), 3.54-3.67 (m, 6H), 3.95 (s, 3H), 6.47 (dd, 1H), 6.87 (d, 1H), 7.0 (m, 1H), 7.09 (m, 2H), 7.47 (m, 2H), 7.68 (m, 1H), 7.92 (m, 2H), 8.18 (m, 2H), 8.53 (s, 1H), 8.75 (s, 1H)

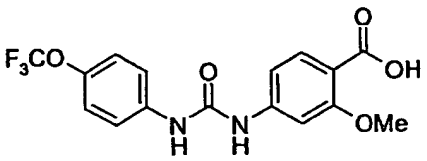
Example 137

***N*-(1-Benzyl-piperidin-4-yl)-4-(3-indan-5-yl-ureido)-2-methoxy-benzamide**



Example 138

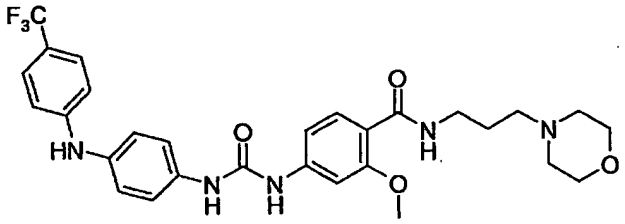
2-Methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzoic acid



Using the same procedure as described in **Ex 45** was the title product synthesised from 4-amino-2-methoxy-benzoic acid and 4-trifluoromethoxyphenyl isocyanate giving the title product.

Example 139

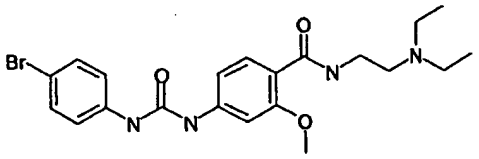
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-{3-[4-(4-trifluoromethyl-phenylamino)-phenyl]-ureido}-benzamide



Following the same general procedure as described in **Ex 88** was **Ex 61** (57 mg, 0.20 mmol) and 4-(4-Trifluoromethyl-phenylamino)-benzoic acid (0.10 g, 0.36 mmol) giving 52 mg (45%) of the title product. LCMS (an20p15): (M+1) = 572 m/z.

Example 140

4-[3-(4-Bromo-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide



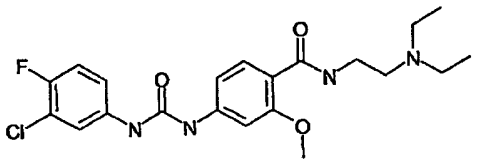
Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 4-Bromophenyl isocyanate.

NMR(DMSO-d_6): δ 0.99 (t, 6H), 3.29 (m, 2H), 3.89 (s, 3H), 8.25 (t, 1H), 8.91(s, 1H), 9.02 (s, 1H)

LC-MS (an20p10); Rt = 5.33 min. (M+1) = 464.9 m/z

Example 141

4-[3-(3-Chloro-4-fluoro-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide

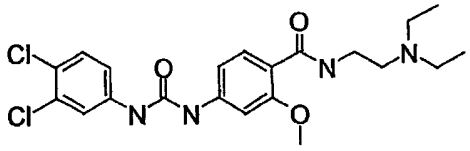


Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 3-Chloro-4-fluoro-phenyl isocyanate.

NMR(DMSO-d_6): δ 0.99 (t, 6 H), 3.90 (s, 3H), 8.25 (t, 1H), 8.97 (s, 1H), 9.08 (s, 1H)

Example 142

4-[3-(3,4-Dichloro-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide



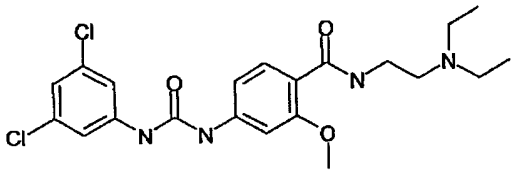
Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 3,4-Dichloro-phenyl isocyanate.

LCMS(an20p10); Rt = 5.63 min. (M+1) = 453 m/z

^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H), 10.32 (s, 1H), 8.26 (s, 1H), 7.93 (s, 1H), 7.80 (d, 1H), 7.52-7.44 (m, 3H), 7.04 (d, 1H), 3.89 (s, 3H), 3.40 (m, 2H), 2.65 (m, 6H), 1.03 (t, 6H)

Example 143

4-[3-(3,5-Dichloro-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide



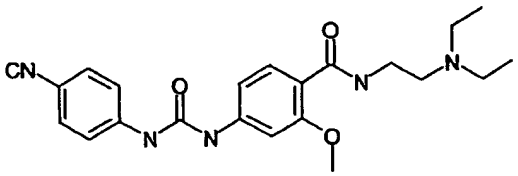
Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 3,5-Dichloro-phenyl isocyanate.

NMR(CDCl3): δ 1.43 (t, 6H), 3.86 (m, 2H), 3.88 (s, 3H), 8.44 (m, 1H), 9.44 (s, 1H), 9.50 (s, 1H)

LC-MS(an20p10): Rt = 5.75 min. (M+1) = 454.9 m/z

Example 144

4-[3-(4-Cyano-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide

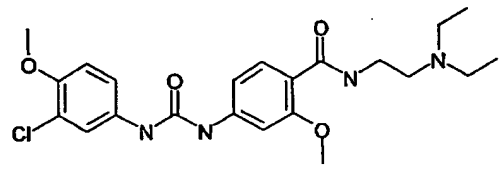


Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 4-Cyano-phenyl isocyanate.

NMR(DMSO-d_6): δ 0.99 (t, 6H), 3.90 (s, 3H), 8.25 (t, 1H), 9.17 (s, 1H), 9.29 (s, 1H)

Example 145

4-[3-(3-Chloro-4-methoxy-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide



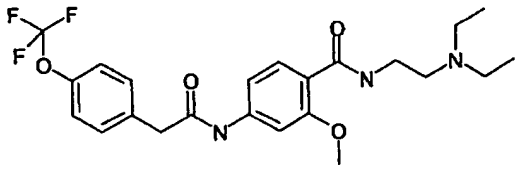
Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 3-Chloro-4-methoxy-phenyl isocyanate.

NMR(CDCl3): δ 1.31 (t, 6H), 3.73 (q, 2H), 3.85 (s, 3H), 8.39 (t, 1H), 9.22 (s, 1H), 9.46 (s, 1H)

LC-MS(an20p10): Rt = 4.92 min. (M+1) = 450.0 m/z

Example 146

N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(4-trifluoromethoxy-phenyl)-acetylamino]-benzamide

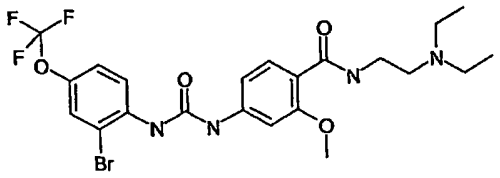


Using the same procedure as described in **Ex 5** was the title product synthesised from **Ex 63** and 4-(trifluoromethoxy)phenylacetic acid.

NMR(CDCl3): δ 1.03 (t, 6H), 3.78 (s, 2H), 3.91 (s, 3H), 8.47 (t, 1H), 8.62 (s,1H)

Example 147

4-[3-(2-Bromo-4-trifluoromethoxy-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide



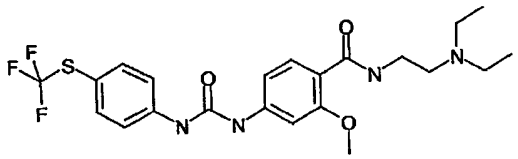
Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 170** and N*1*,N*1*-Diethyl-ethane-1,2-diamine.

NMR(CDCl3): δ 1.03 (t, 6H), 3.91 (s, 3H), 8.33 (s, 1H), 9.83 (s,1H)

LC-MS(an20p10): Rt = 6.10 min. (M+1) = 548.0 m/z

Example 148

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethylsulfanyl-phenyl)-ureido]-benzamide

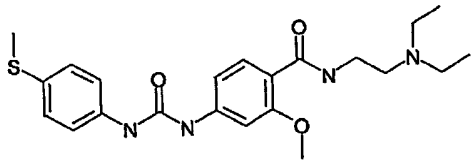


Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 4-trifluoromethylsulfanyl-phenyl isocyanate.

NMR(DMSO-d_6): δ 0.99 (t, 6H), 3.90 (s, 3H), 8.25 (t, 1H), 9.12 (s, 1H), 9.16 (s, 1H)

Example 149

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-methylsulfanyl-phenyl)-ureido]-benzamide

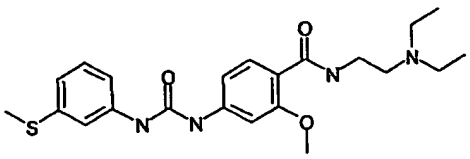


Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 4-methylsulfanyl-phenyl isocyanate.

NMR(DMSO-d_6): δ 0.99 (t, 6H), 3.89 (s, 3H), 8.25 (t.1H), 8.79 (s, 1H), 8.99 (s, 1H)

Example 150

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-methylsulfanyl-phenyl)-ureido]-benzamide



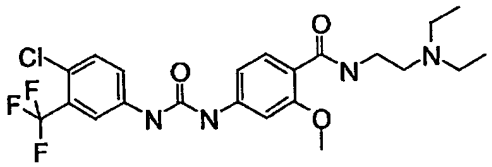
Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 3-methylsulfanyl-phenyl isocyanate.

NMR(CDCl3): δ 1.26 (t, 6H), 2.45 (s, 3H), 3.68 (m, 2H), 3.84 (s, 3H), 8.38 (t, 1H), 9.35 (s, 1H), 9.57 (s, 1H)

LC-MS(an20p10): Rt = 5.05 min. (M+1) = 431.0 m/z

Example 151

4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-N-(2-diethylamino-ethyl)-2-methoxy-benzamide



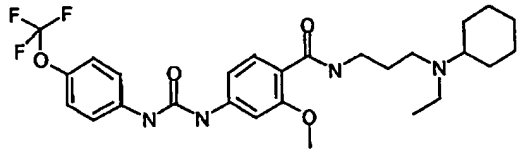
Using the same procedure as described in **Ex 64** was the title product synthesised from **Ex 63** and 4-Chloro-3-trifluoromethyl-phenyl isocyanate.

LCMS(an20p10); Rt = 5.83 min. (M+1) = 487 m/z

^{1}H-NMR (DMSO-d_6): δ 9.85 (s, 1H), 9.74 (s, 1H), 9.29 (br s, 1H), 8.39 (t, 1H), 8.15 (s, 1H), 7.81-7.52 (m, 4H), 7.05 (d, 1H), 3.90 (s, 3H), 3.64 (m, 2H), 3.23 (m, 6H), 1.22 (m, 6H).

Example 152

N-[3-(Cyclohexyl-ethyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

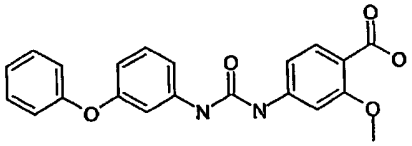


Using the same procedure as described in **Ex 48** was the title product synthesised from **Ex 138** and N*1*-Cyclohexyl-N*1*-ethyl-propane-1,3-diamine (synthesized as described in **Ex 66** using Bromopropyl phtalimide and Cyclohexyl-ethyl-amine)

NMR(CDCl3): 0.95 (t,3H), 3.87 (s,3H), 8.05 (s, 1H), 9.17 (m, 2H)

Example 153

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzoic acid



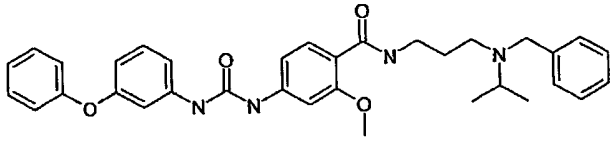
Using the same procedure as described in **Ex 9** was the title product synthesised from 4-amino-2-methoxy benzoic acid and 3-Phenoxyphenylisocyanate.

^{1}H-NMR (DMSO-d_6): δ 12.07 (br s, 1H), 9.02 (s, 1H), 8.93 (s, 1H), 7.66 (d, 1H), 7.40 (m, 3H), 7.29 (m, 2H), 7.15 (m, 2H), 7.03 (m, 2H), 6.95 (dd, 1H), 6.64 (dd, 1H), 3.79 (s, 3H)

LC-MS(an20n15): t r= 8.8 min. (M-1) = 377.0 m/z

Example 154

N-[3-(Benzyl-isopropyl-amino)-propyl]-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide



Using the same procedure as described in **Ex 10** was the title product synthesised from **Ex 138** and N*1*-Benzyl-N*1*-isopropyl-propane-1,3-diamine (synthesized as described in example 77 using Bromopropyl phtalimide and Benzyl-isopropyl-amine)

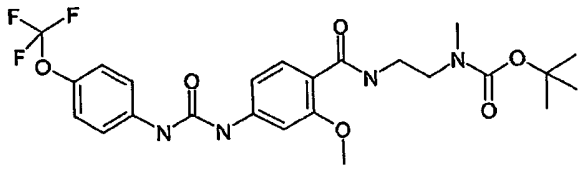
^{1}H-NMR ($CDCl_3$): δ 9.88 (s, 1H), 9.66 (s, 1H), 8.63 (s, 1H), 8.15 (t, 1H), 7.81 (d, 1H), 7.50 (d, 1H), 7.45 (t, 1H), 7.39 (m, 2H), 7.29 (m, 6H), 7.05 (m, 2H), 6.97 (m, 2H), 6.61 (m, 1H), 3.94 (s, 2H),

3.80 (s, 3H), 3.37 (m, 3H), 2.87 (t, 2H), 1.91 (t, 2H), 1.26 (d, 6H)

LC-MS(an20p15): t r= 6.3 min. (M+1) = 567.1 m/z

Example 155

(2-{2-Methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzoylamino}-ethyl)-methyl-carbamic acid tert-butyl ester



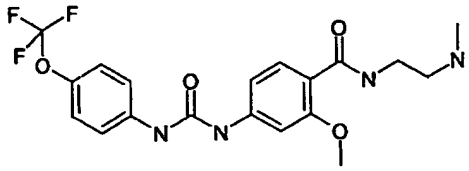
Using the same procedure as described in **Ex 48** was the title product synthesised from **Ex 138** and commercially available (2-Amino-ethyl)-methyl-carbamic acid tert-butyl ester

NMR(CDCl3): δ 1.41 (s, 9H), 2.90 (s, 3H), 3.96 (s, 3H), 8.55 (s, 1H), 8.61 (1H)

LC-MS(an20p10): Rt = 8.81 min. (M+1) = 527.1 m/z

Example 156

2-Methoxy-N-(2-methylamino-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

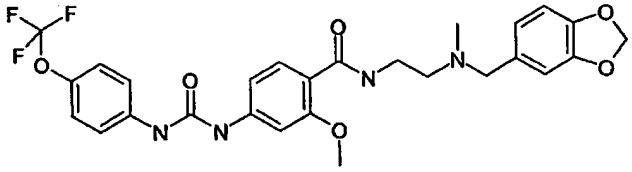


Ex 155 (0.7g, 1.33 mmol) was suspended in EtOAc and cooled to 0°C before anhydrous hydrogenchloride was bubbled through the solution for 10 min. Stirring was continued for 1h before the volatiles were removed *in vacuo*. The residue was partitioned between Sat, $NaHCO_3$-solution (100 ml) and DCM (100 ml). The aqueous phase was extracted with DCM (3 x 70 ml). The combined organic extracts were dried over $MgSO_4$. Solvent was removed *in vacuo* to give the title compound **Ex 156** (0.52g, 1.22 mmol, 92%).

NMR(CDCl3): δ 2.46 (s, 3H), 3.92 (s, 3H), 8.49 (t, 1H), 8.82(s, 1H), 8.83 (s, 1H)

Example 157

N-[2-(Benzo[1,3]dioxol-5-ylmethyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide



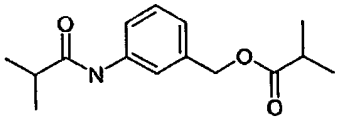
To a solution of piperonylalcohol (36 mg, 0.235 mmol) in THF (30 ml) were successively added triphenylphosphine (92 mg, 0.352 mmol), **Ex 156** (100 mg, 0.235 mmol) and DIAD (68 µl, 0.352 mmol). The mixture was stirred overnight at room temperature under N_2. The reaction mixture was partitioned between sat. $NaHCO_3$-solution (100 ml) and EtOAc (100 ml). The aqueous phase was extracted with EtOAc (3 x 70 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified over silica gel chromatography (eluted with DCM/MeOH/NH_3 (100:10:1)) to give the title compound **Ex 157** (8.8mg, 0.016 mmol, 6.8%)

NMR(CDCl3): δ 2.23 (s,3H), 3.44 (s, 2H), 3.95 (s, 3H), 5.89 (s, 2H), 8.78 (s, 1H), 8.90 (s, 1H)

LC-MS(an20p10): Rt = 6.10 min. (M+1) = 561.1 m/z

Example 158

Isobutyric acid 3-isobutyrylamino-benzyl ester

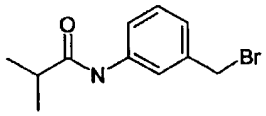


A solution of 3-aminobenzyl alcohol (1g, 8.32 mmol), isobutyric anhydride (2.69 ml, 16.4 mmol) and DMAP (0.05g, 0.4 mmol) in dry dichloromethane (30 ml) was stirred overnight at room temperature. Solvent was removed in vacuo to give a residue which was partitionned between ethyl acetate and 1N aq. HCl solution. The organic phase was washed with 1N aq. HCl (2x), sat.aq. NaHCO3, brine and dried over MgSO4 to give the title compound **Ex 158** as a pale brown oil (2.19g, 8.32 mmol, 100%).

NMR(CDCl3): δ 1.20 (d, 6H), 1.25 (d, 6H), 2.55 (m, 2H), 5.09 (s, 2H), 7.09 (d, 1H), 7.28 – 7.56 (m, 4H)

Example 159

N-(3-Bromomethyl-phenyl)-isobutyramide

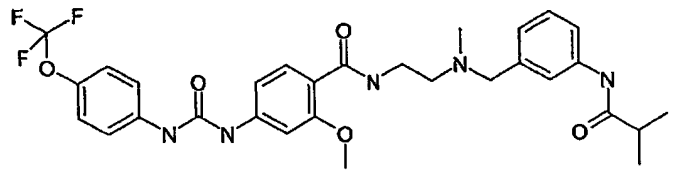


To a solution of **Ex 158** (2.19g, 8.32 mmol) in dry dichloromethane (25 ml) was added a 30% solution of HBr in acetic acid (85 ml, excess). The reaction mixture was stirred for 3 days at room temperature. The mixture was then poured onto ice (400g) and extracted with dichloromethane. The organic phase was washed with water (1x), sat. aq. NaHCO3, brine, dried over MgSO4 and concentrated in vacuo to give the title compound **Ex 159** as a white solid (1.9g, 7.4 mmol, 84%).

NMR(CDCl3): δ 1.25 (d, 6H), 2.51 (m, 1H), 4.44 (s, 1H), 7.11 (d, 1H), 7.25 – 7.43 (m, 3H), 7.66 (s, 1H).

Example 160

N-{2-[(3-Isobutyrylamino-benzyl)-methyl-amino]-ethyl}-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide



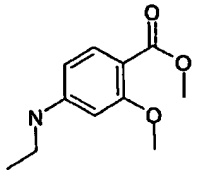
To a solution of **Ex 156** (50 mg, 0.117 mmol) and potassium carbonate (excess) in DMF (7 ml) was added **Ex 159** (30 mg, 0.117 mmol). The mixture was refluxed at 70°C overnight under N_2. The reaction mixture was partitioned between a 2 M $NaHSO_3$-solution (20 ml) and EtOAc (20 ml). The aqueous phase was extracted with EtOAc (2 x 20 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified over silica gel chromatography (eluted with DCM/MeOH/NH_3 (100:10:1)) to give the title compound **Ex 160** (17.1mg, 0.028 mmol, 24%)

NMR(CDCl3): δ 1.20 (d, 6H), 2.23 (s, 3H), 3.86 (s, 3H), 8,53 (t, 1H), 8.67(s, 1H), 8.76 (s, 1H)

LC-MS(an20p10): Rt = 6.16 min. (M+1) = 602.2 m/z

Example 161

4-Ethylamino-2-methoxy-benzoic acid methyl ester

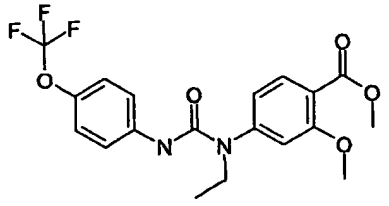


Using the same procedure as described in **Ex 30** was the title product synthesised from acetyldehyde and methyl 4-amino-2-methoxybenzoate

^{1}H-NMR ($CDCl_3$): δ 7.73 (d, 1H), 6.13 (dd, 1H), 6.06 (d, 1H), 4.25 (br s, 1H), 3.83 (s, 3H), 3.80 (s,3H), 3.18 (q, 2H), 1.24 (t, 3H)

Example 162

4-[1-Ethyl-3-(4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

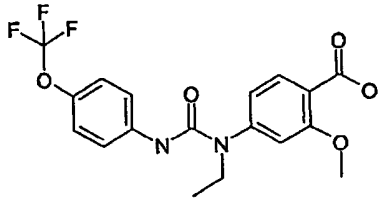


Using the same procedure as described in example 31 was the title product synthesised from **Ex 161** and 4-trifluoromethoxyphenylisocyanate

^{1}H-NMR ($CDCl_3$): δ 7.82 (d, 1H), 7.35 (m, 2H), 7.06 (d, 2H), 6.87 (m, 2H), 6.54 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.77 (q, 2H), 1.15 (t, 3H)

Example 163

4-[1-Ethyl-3-(4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzoic acid

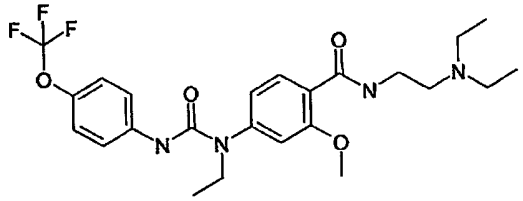


Using the same procedure as described in example 32 was the title product synthesised from **Ex 162**

^{1}H-NMR ($CDCl_3$): δ 10.40 (br s, 1H), 8.18 (d, 1H), 7.42 (m, 2 H), 7.13 (m, 3H), 7.00 (d, 1H), 6.58 (s, 1H), 4.10 (s, 3H) 3.86 (q, 2H), 1.23 (t, 3H)

Example 164

N-(2-Diethylamino-ethyl)-4-[1-ethyl-3-(4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzamide



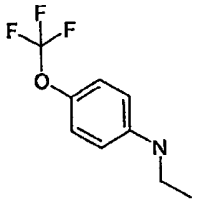
Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 163** and N*1*,N*1*-Diethyl-ethane-1,2-diamine

^{1}H-NMR ($CDCl_3$): δ 8.48 (br s, 1H), 8.30 (d, 1H), 7.34 (m, 2H), 7.11 (d, 2H), 7.03 (dd, 1H), 6.90 (d, 1H), 6.26 (s, 1H), 4.00 (s, 3H), 3.83 (q, 2H), 3.64 (m, 2H), 2.74 (m, 6H), 1.18 (m, 9H)

LC-MS(an20p15): t r= 4.2 min. (M+1) = 497.0 m/z

Example 165

Ethyl-(4-trifluoromethoxy-phenyl)-amine

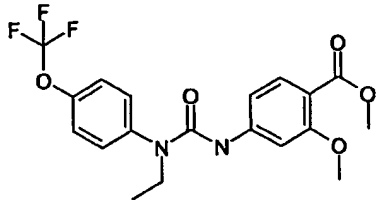


Using the same procedure as described in **Ex 30** was the title product synthesised from acetyldehyde and 4-trifluoromethoxyaniline

^{1}H-NMR ($CDCl_3$): δ 7.08 (m, 2H), 6.58 (m, 2H), 3.62 (br s, 1H), 3.16 (q, 2H), 1.29 (t, 3H)

Example 166

4-[3-Ethyl-3-(4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

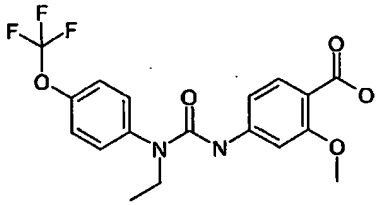


Using the same procedure as described in **Ex 169** was the title product synthesised from **Ex 165** and methyl 4-amino-2-methoxybenzoate

^{1}H-NMR ($CDCl_3$): δ 7.69 (d, 1H), 7.52 (d, 1H), 7.33 (s, 4H), 6.49 (dd, 1H), 6.32 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.77 (q, 2H), 1.17 (t, 3H)

Example 167

4-[3-Ethyl-3-(4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzoic acid

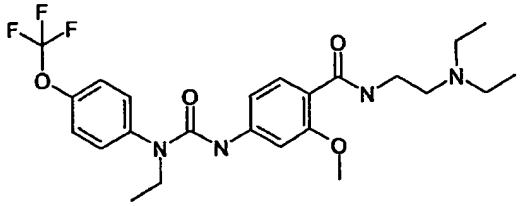


Using the same procedure as described in **Ex 32** was the title product synthesised from **Ex 166**

^{1}H-NMR ($CDCl_3$): δ 10.44 (br s, 1H), 7.90 (d, 1H), 7.80 (d, 1H), 7.35 (s, 4H), 6.50 (m, 2H), 4.05 (s, 3H), 3.78 (q, 2H), 1.19 (t, 3H)

Example 168

N-(2-Diethylamino-ethyl)-4-[3-ethyl-3-(4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzamide

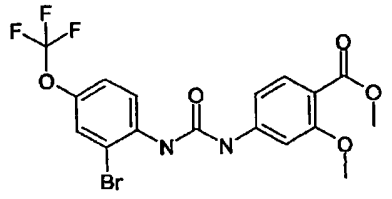


Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 167** and N*1*,N*1*-Diethyl-ethane-1,2-diamine

^{1}H-NMR ($CDCl_3$): δ 8.43 (br t, 1H), 8.02 (d, 1H), 7.72 (d, 1H), 7.37 (s, 4H), 6.41 (dd, 1H), 6.22 (s, 1H), 4.00 (s, 3H), 3.80 (q, 2H), 3.62 (m, 2H), 2.72 (m, 6H), 1.17 (m, 9H)

Example 169

4-[3-(2-Bromo-4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

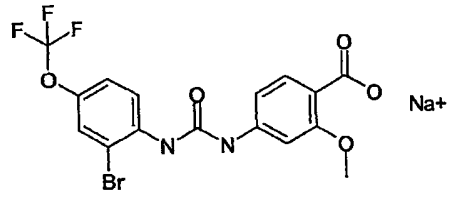


To a cooled (0°C) solution of phosgene (20% solution in toluene, 2.76 ml, 5.52 mmol) in dry dichloromethane (75 ml) was added, under an argon atmosphere, methyl 4-amino-2-methoxybenzoate (1g, 5.52 mmol) in one portion, followed by a dropwise addition of diisopropylethylamine (1.92 ml, 11.04 mmol). The mixture was stirred for 15 minutes at 0°C prior to the addition of 2-bromo-4(trifluoromethoxy)aniline (0.83 ml, 5.52 mmol). The reaction mixture was stirred at 0°C for a further 2 hours and then was allowed to stir at room temperature overnight. The organic phase was washed with 1N aq. HCl (2x), sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue which was recrystallized in hot acetonitrile. The fine crystalline solid was filtered off, washed with cold acetonitrile and dried *in vacuo* to give the title compound **Ex 169** as a pale-orange solid (1.64g, 3.54 mmol, 64%).

^{1}H-NMR (DMSO-d_6): δ 3.74 (s, 3H), 3.80 (s, 3H), 7.02 (d, 1H), 7.38 (s, 1H), 7.42 (d, 1H), 7.69 (d, 1H), 7.74 (s, 1H), 8.17 (d, 1H), 8.36 (s, 1H), 9.85 (s, 1H)

Example 170

4-[3-(2-Bromo-4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-benzoic acid, sodium salt

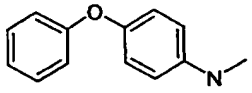


A solution of **Ex 169** (1.38g, 2.98 mmol) and $LiOH.H_2O$ (0.25g, 5.96 mmol) in a THF/water mixture (40ml/13ml) was stirred at 40°C for 24 hours. THF was removed in vacuo. The aqueous phase was left overnight at room temperature. A white solid crystallized out. The solid was filtered off, washed with several portions of cold water and dried *in vacuo* to give the title compound **Ex 170** as a white solid (1.2g, 2.54 mmol, 86%).

^{1}H-NMR (DMSO-d_6): δ 3.7 (s, 3H), 6.96 (d, 1H), 7.31 (s, 1H), 7.38 (d, 1H), 7.49 (d, 1H), 7.69 (s, 1H), 8.05 (d, 1H), 9.30 (bs, 1H), 10.57 (bs, 1H)

Example 171

Methyl-(4-phenoxy-phenyl)-amine

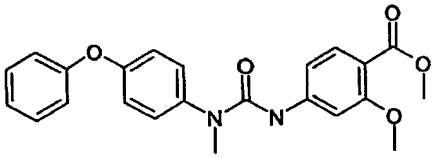


Using the same procedure as described in **Ex 30** was the title product synthesised from 4-phenoxyaniline

^{1}H-NMR ($CDCl_3$): δ 2.86 (s, 3H), 6.63 (d, 2H), 6.93 – 7.32 (m, 8H)

Example 172

2-Methoxy-4-[3-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid methyl ester

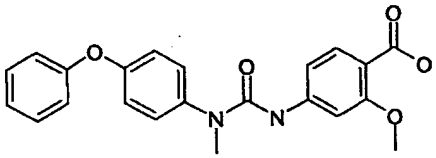


Using the same procedure as described in **Ex 169** was the title product synthesised from **Ex 171** and methyl 4-amino-2-methoxybenzoate

^{1}H-NMR ($CDCl_3$): δ 3.32 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.44 (m, 2H), 7.07 – 7.73 (m, 11H)

Example 173

2-Methoxy-4-[3-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid

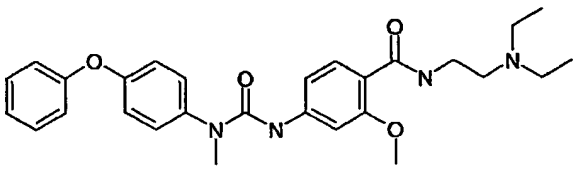


Using the same procedure as described in **Ex 32** was the title product synthesised from **Ex 172**

^{1}H-NMR ($CDCl_3$): δ 3.35 (s, 3H), 4.11 (s, 3H), 6.42 (dd, 1H), 6.54 (s, 1H), 7.09 – 7.46 (m, 9H), 7.98 (m, 2H)

Example 174

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide

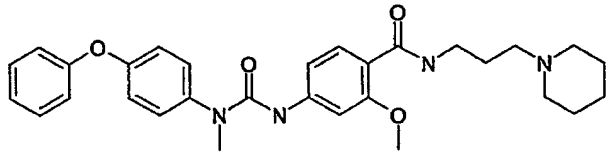


Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 173** and N*1*,N*1*-Diethyl-ethane-1,2-diamine

NMR(CDCl3): δ 1.11 (s, 6H), 2.67 (m, 6H), 3.35 (s, 3H), 3.40 (s, 3H), 8.06 (d, 1H), 8.10 (d, 1H)

Example 175

2-Methoxy-4-[3-methyl-3-(4-phenoxy-phenyl)-ureido]-N-(3-piperidin-1-yl-propyl)-benzamide

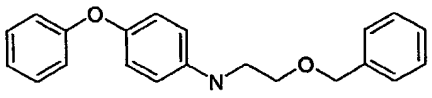


Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 173** and 3-Piperidin-1-yl-propylamine

NMR(CDCl3): δ 2.45 (m, 6H), 3.34 (s,3H), 3.40 (s, 3H), 7.94 (t, 1H), 8.00 (d, 1H)

Example 176

(2-Benzyloxy-ethyl)-(4-phenoxy-phenyl)-amine

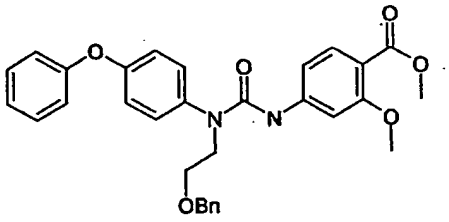


A mixture of 4-phenoxyaniline (1g, 5.40 mmol) and benzaloxyacetaldehyde (0.76ml, 5.40 mmol) in methanol (6 ml) was stirred at 0°C for 30 minutes prior to the dropwise addition of sodium cyanoborohydride (0.339g, 5.40 mmol). The reaction mixture ws stirred overnight at room temperature. Solvent was removed *in vacuo*. The residue was partitioned between dichloromethane and brine. The aqueous phase was extracted with dichloromethane. The combined organic phases was dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified over silicagel chromatography (EtOAc/Heptane: 1/9 to 1/1 in 20 min.) to give the title compound **Ex 176** (0.74g, 2.32 mmol, 43%).

NMR(CDCl3): δ 3.34 (t, 2H), 3.74 (t, 3H), 4.59 (s, 2H), 6.66 (d, 2H), 6.91 – 7.38 (m, 13H)

Example 177

4-[3-(2-Benzyloxy-ethyl)-3-(4-phenoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

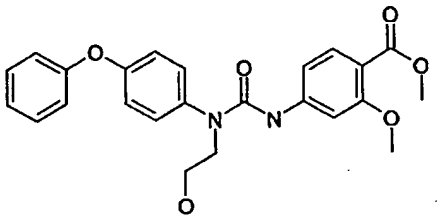


Using the same procedure as described in **Ex 169** was the title product synthesised from **Ex 176** and methyl 4-amino-2-methoxybenzoate

NMR(CDCl3): δ 3.74 (t, 2H), 4.11 (s, 3H), 4.13 (s, 3H), 3.97 (t, 2H), 4.58 (s, 2H), 6.37 (d, 1H), 7.03 – 7.43 (m, 15H), 7.54 (s, 1H), 7.7 (d, 1H)

Example 178

4-[3-(2-Hydroxy-ethyl)-3-(4-phenoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester

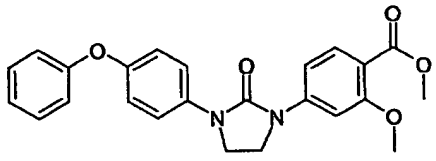


To a solution of **Ex 177** (830mg, 1.57 mmol) in methanol (80ml) was added 10% $Pd(OH)_2/C$ (10%w/w, 83mg). The reaction mixture was stirred for 5 hours at 30°C under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give the title compound **Ex 178** as a colourless oil (643mg, 1.47 mmol, 93%)

^{1}H-NMR ($CDCl_3$): δ 3.84 (m+s, 5H), 3.9 (m+s, 5H), 6.45 (m, 1H), 7.09 – 7.45 (m, 9H), 7.51 (s, 1H), 7.74 (d, 1H)

Example 179

2-Methoxy-4-[2-oxo-3-(4-phenoxy-phenyl)-imidazolidin-1-yl]-benzoic acid methyl ester



To a cooled (0°C) solution of **Ex 178** (640mg, 1.47 mmol) in dry dichloromethane (15ml) were successively added, under an argon atmosphere, methanesulfonyl chloride (0.11ml,

1.47 mmol) and diisopropylethylamine (0.26ml, 1.47 mmol). The reaction mixture was stirred for 2 hours at 0°C and then was allowed to stir at room temperature overnight. Solvent was removed in vacuo. The crude was chromatographed over silica gel to give 4-[3-(2-Methanesulfonyloxy-ethyl)-3

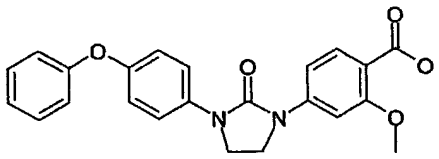
-(4-phenoxy-phenyl)-ureido]-2-methoxy-benzoic acid methyl ester (200mg, 0.39 mmol) which was dissolved in dry acetonitrile (10ml). Triethylamine (0.54ml, 3.90 mmol) was added and the reaction mixture was stirred at 70°C for 2 hours. Solvent was removed in vacuo. The residue was purified over silica gel chromatography (EtOAc/Heptane: 1/9 to 4/1 in 30 min.) to give the title compound **Ex 179** (100mg, 0.24 mmol, 16%).

^{1}H-NMR ($CDCl_3$): δ 3.87 (s, 3H), 3.9 (s, 3H), 4.09 (t, 2H), 4.53 (t, 2H), 6.69 (s, 1H), 6.75 (d, 1H), 7.01 – 7.72 (m, 9H), 7.81 (d, 1H).

LC-MS(an20p15): Rt = 7.34 min. (M+1) = 419 m/z

Example 180

2-Methoxy-4-[2-oxo-3-(4-phenoxy-phenyl)-imidazolidin-1-yl]-benzoic acid

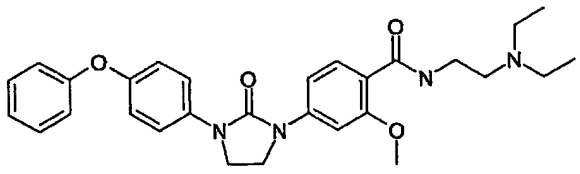


Using the same procedure as described in **Ex 32** was the title product synthesised from **Ex 179**

^{1}H-NMR ($CDCl_3$): δ 3.72 (t, 2H), 4.06 (t, 2H), 4.11 (s, 3H), 6.42 (d, 1H), 6.48 (s, 1H), 7.1 – 7.47 (m, 8H) – 7.92 (s, 1H), 8.0 (d, 1H)

Example 181

N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(4-phenoxy-phenyl)-imidazolidin-1-yl]-benzamide



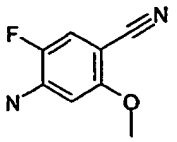
Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 180** and N*1*,N*1*-Diethyl-ethane-1,2-diamine

^{1}H-NMR ($CDCl_3$): δ 1.28 (br t, 6H), 3.0 (m, 6H), 3.8 (m, 2H), 3.97 (s, 3H), 4.05 (t, 2H), 4.5 (t, 2H), 6.68 (s, 1H), 6.8 (d, 1H), 6.95 – 7.35 (m, 7H), 7.68 (d, 2H), 8.05 (d, 1H), 8.5 (br s, 1H)

LC-MS(an20p10): Rt = 4.75 min. (M+1) = 503 m/z

Example 182

4-Amino-5-fluoro-2-methoxy-benzonitrile

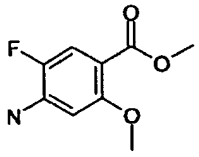


To a cooled (0°C) solution of methanol (5.2ml, 130.0 mmol) in anhydrous THF (30ml) was added, under an argon atmosphere, a 1M solution of *tert* BuOK in THF (25.9ml, 25.9 mmol). After stirring for 5 minutes at room temperature, 4-amino-2,5-difluoro-benzonitrile (2g, 13.0 mmol) was added to the solution in one portion. The reaction mixture was then heated to 70°C and stirred for 2h 30 minutes. After cooling, diethyl ether was added. The organic phase was washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was chromatographed over silica gel (EtOAc/Heptane: 1/9 to 1/1) to give the title compound **Ex 182** as a pale-yellow solid (1.58g, 9.51 mmol, 73%).

^{1}H-NMR ($CDCl_3$): δ 3.84 (s, 3H), 4.26 (br s, 2H), 6.27 (d, 1H), 7.12 (d, 1H)

Example 183

4-Amino-5-fluoro-2-methoxy-benzoic acid methyl ester

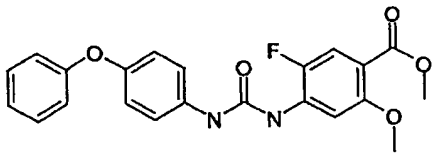


To a saturated solution of gas hydrogen chloride in methanol (20ml) and water (0.04ml) was added **Ex 182** (290mg, 1.74 mmol). The reaction mixture was stirred overnight at 40°C and then at 70°C for 5 hours. Solvent was removed *in vacuo*. The residue was partitioned between sat.aq. $NaHCO_3$ and dichloromethane. The aqueous phase was extracted with dichloromethane (2x). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* .The crude was purified over silica gel chromatography (EtOAc/Heptane: 1/9 to 1/1) to give the title compound **Ex 183** as a white solid (60mg, 0.30 mmol, 17%).

^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 3H), 3.84 (s, 3H), 6.3 (d, 1H), 7.56 (d, 1H)

Example 184

5-Fluoro-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureIdo]-benzoic acid methyl ester

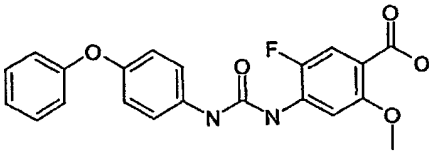


Using the same procedure as described in example 190 was the title product synthesised from **Ex 183** and 4-phenoxyaniline

^{1}H-NMR (DMSO-d_6): δ 3.76 (s, 3H), 3.79 (s, 3H), 6.95 – 7.57 (m, 10H), 8.15 (d, 1H), 8.85 (s, 1H), 9.15 (s, 1H)

Example 185

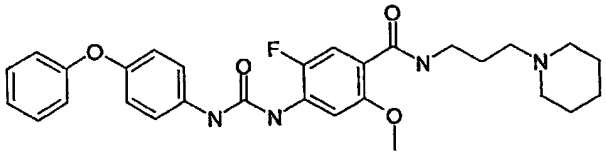
5-Fluoro-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzoic acid



Using the same procedure as described in example 32 was the title product synthesised from **Ex 184. Ex 185** was used without characterization in **Ex 186.**

Example 186

5-Fluoro-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-N-(3-piperidin-1-yl-propyl)-benzamide



Using the same procedure as described in **Ex 33** was the title product synthesised from **Ex 185** and 3-Piperidin-1-yl-propylamine

^{1}H-NMR ($CDCl_3$): δ 1.4 – 1.9 (m, 8H), 2.4 (m, 6H), 3.5 (m, 2H), 3.95 (s, 3H), 6.98 – 7.45 (m, 8H), 7.86 (d, 1H), 8.28 (m, 2H), 8.54 (s, 1H), 9.02 (s, 1H)

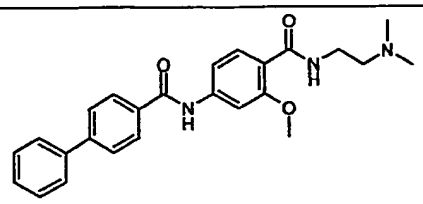
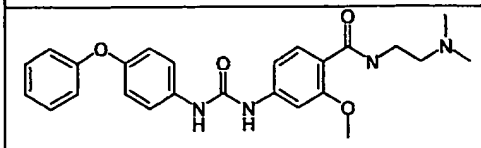
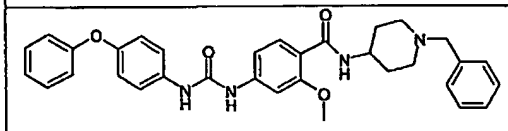
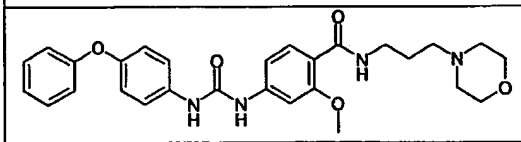
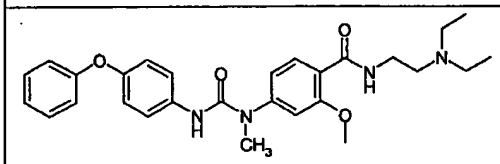
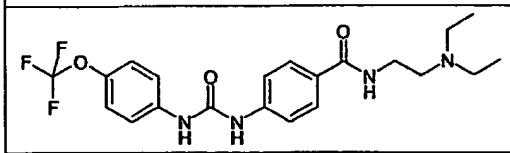
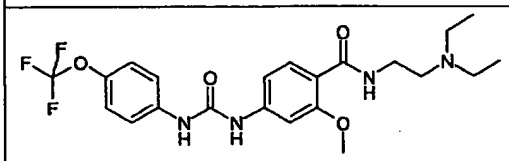
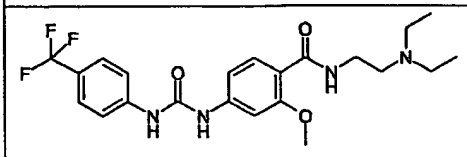
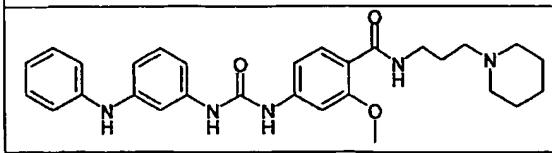
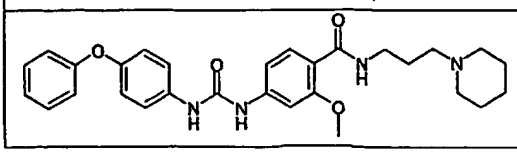
LC-MS(an20p15): Rt = 6.71 (M+1) = 521 m/z

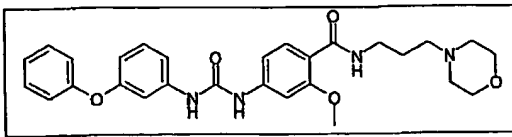
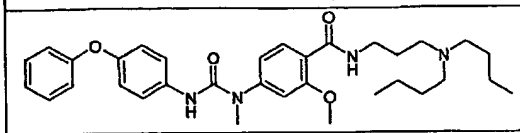
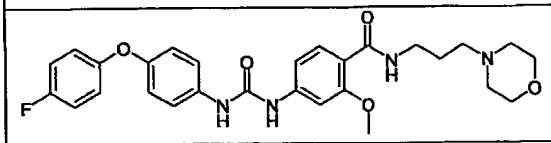
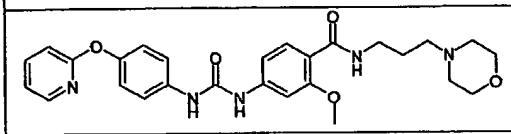
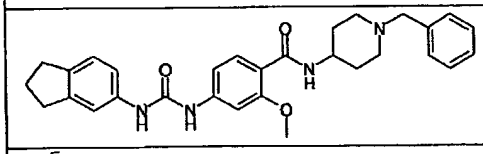
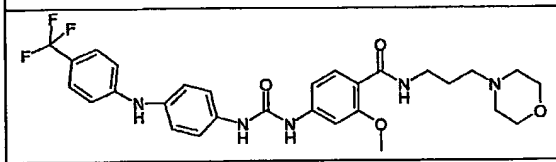
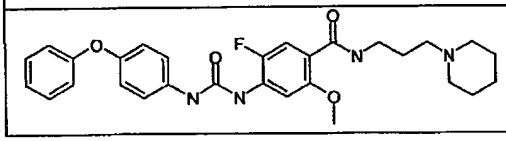
Example 187

***In vitro* tests of compounds according to the invention**

The following results were obtained

Receptor binding data

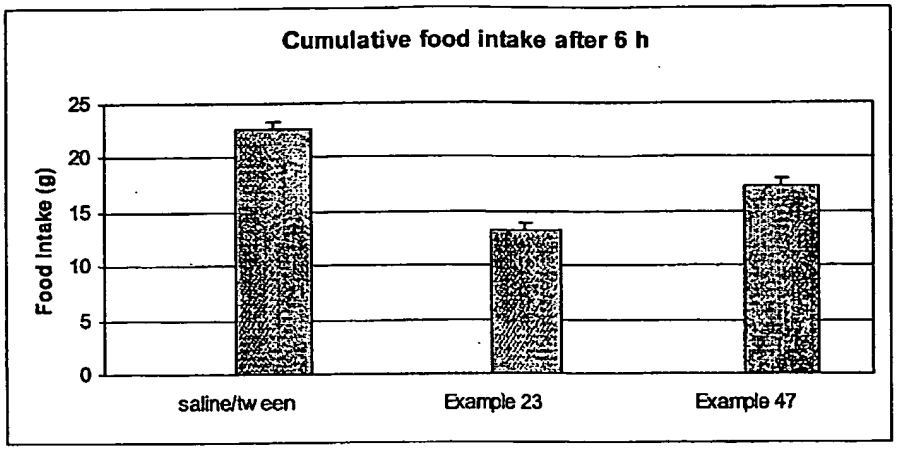
Compound	Example	Receptor binding IC_{50} µM	IP3 IC_{50} µM
	**Ex 2**	1.48	
	**Ex 8**	0.38	2.3
	**Ex 16**	0.22	1.8
	**Ex 23**	0.21	0.77
	**Ex 33**	0.048	0.29
	**Ex 47**	0.07	0.29
	**Ex 48**	0.096	0.19
	**Ex 67**	0.027 (SPA)	0.22
	**Ex 89**	0.012	0.022
	**Ex 95**	0.044	0.24

	Ex 121	0.074	0.11
	Ex 134	0.069	0.67
	Ex 135	0.45	1.6
	Ex 136	4.45	
	Ex 137	0.30	
	Ex 139	1.41	
	Ex 186	1	

Example 188

***In vivo* tests of compounds according to the invention**

The following results were obtained on reduction in food intake.



The following compounds are prepared as described in previous examples.

The following compounds are prepared as described in previous examples.

4-[3-(3-Chloro-phenyl)-ureido]-*N*-(2-dimethylamino-ethyl)-2-methoxy-benzamide

N-(2-Dimethylamino-ethyl)-2-methoxy-4-(3-phenyl-ureido)-benzamide

N-(2-Diethylamino-ethyl)-2-methoxy-4-(3-phenyl-ureido)-benzamide

N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide

N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-{3-[4-(3-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-(3-phenyl-ureido)-benzamide

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-(3-phenyl-1-methyl-ureido)-benzamide

4-[3-(4-Chloro-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(4-Chloro-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

2-Methoxy-4-[3-(4-methoxy-phenyl)-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide

2-Methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Chloro-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Chloro-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Iodo-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Iodo-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(4-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-benzamide

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-iodo-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-iodo-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(3-phenyl-ureido)-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(3-phenyl-1-methyl-ureido)-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-iodo-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-iodo-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

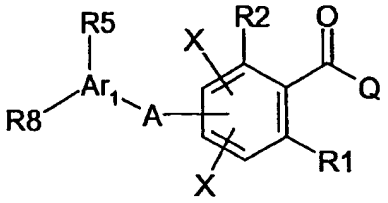
N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(4-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-(1-methyl-3-phenyl-ureido)-benzamide

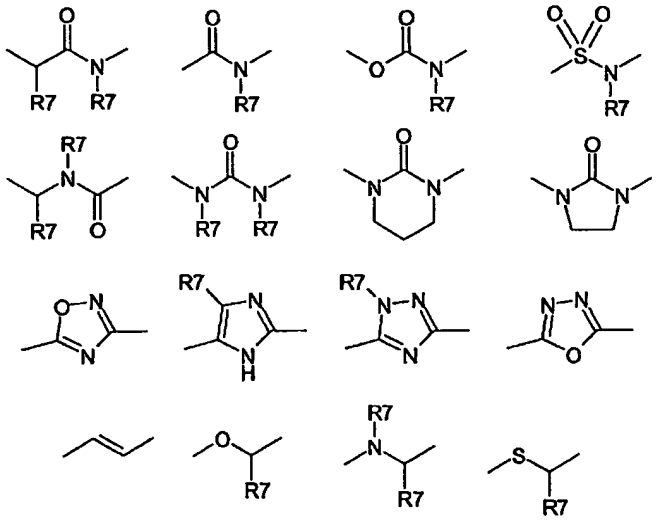
N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-(3-phenyl-ureido)-benzamide

CLAIMS

1. A compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



and, wherein the linker -A- may be attached *via* either of the two free bonds to the Ar_1 group;

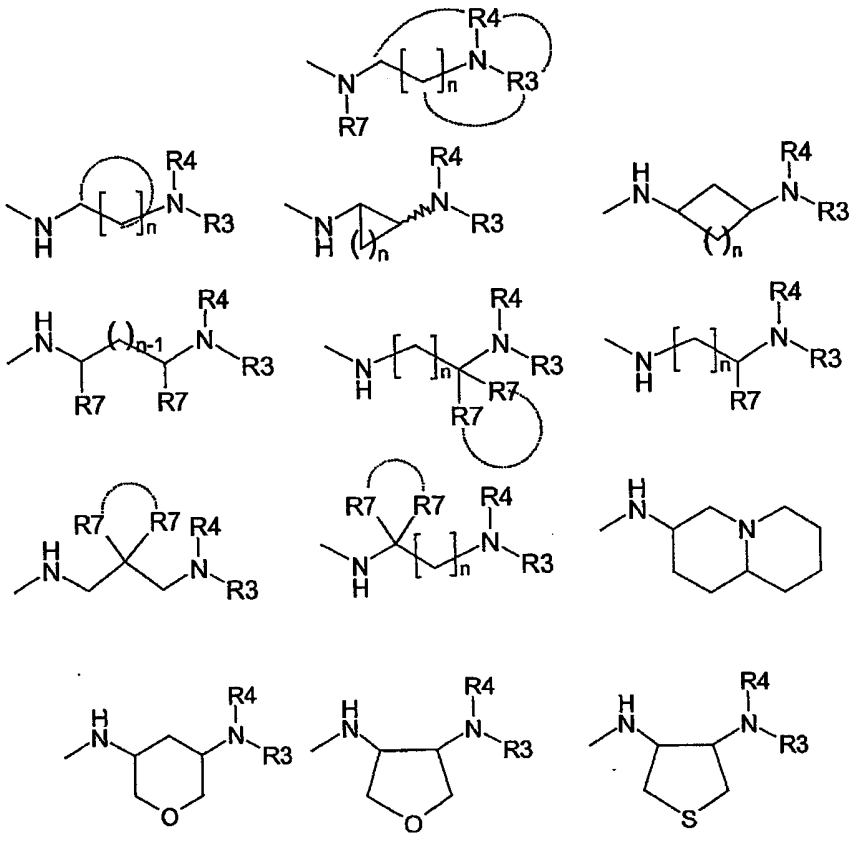
and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

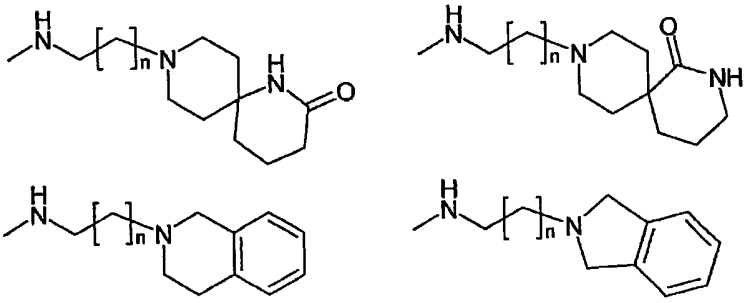
Ar_1 is an aryl or heteroaryl group such as, *e.g.* phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

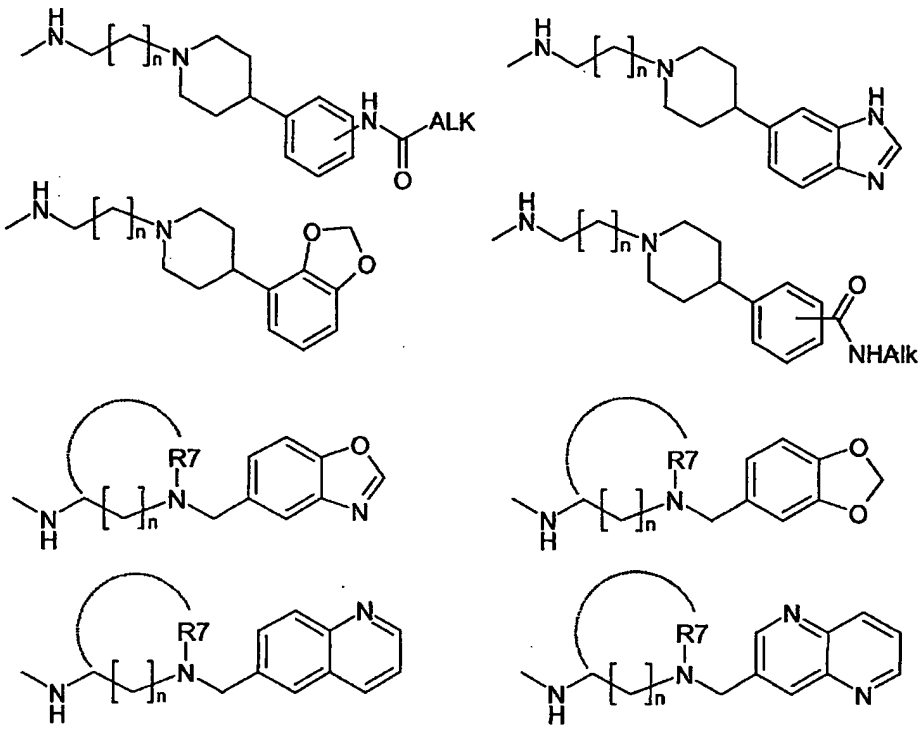
R1 is a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon.

R2 is an R1 group or hydrogen, an OH or an NH_2 group,

Q is selected from the group consisting of







5

R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbon atoms; alkylcycloalkyl with 4-9 carbon atoms; alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-
10 propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, -$CONH_2$, -CONHAlk, -$CONAlk_2$, aryl, substituted aryl, benzyl, substituted benzyl groups

Alk is the same or a different alkyl, alkenyl or alkynyl group;

15

R3 and R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

20 R5 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -SCH_3, partially or fully fluorinated alkyl,

alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2NAlk_2$, $-SO_2Alk$;

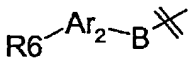
more than one R5 group, same or different, may be present on Ar_1; when more than one R5 or when one R5 and one R8 group are present they could be connected to each other, directly or with a suitable connecting moiety, to form rings;

X being the same or different H, F, Cl, Br, I, $-SCH_3$, $-CF_3$, $-OCF_3$, $-SCF_3$, OCH_3, or lower alkyl or alkenyl group;

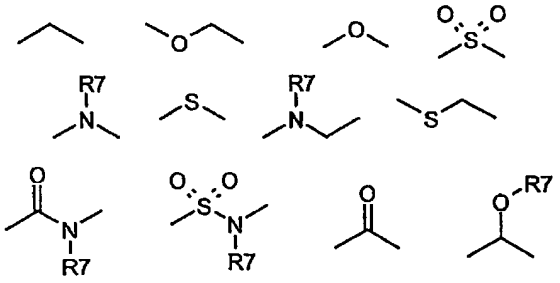
n is 1,2 or 3,

R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (*e.g.* $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr $-CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$;

or R8 has the structure



in which B is a single bond or a connecting moiety selected from the group consisting of:



which may be attached *via* either of the two free bonds to the Ar_1 group;

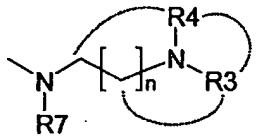
Ar_2 is an aryl or heteroaryl group such as e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole,

quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

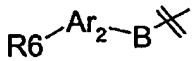
R6 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

more than one R6 group, same or different, may be present on Ar_2; when more than one R6 group is present they could be connected to each other to form rings.

2. A compound according to claim 1, wherein Q is

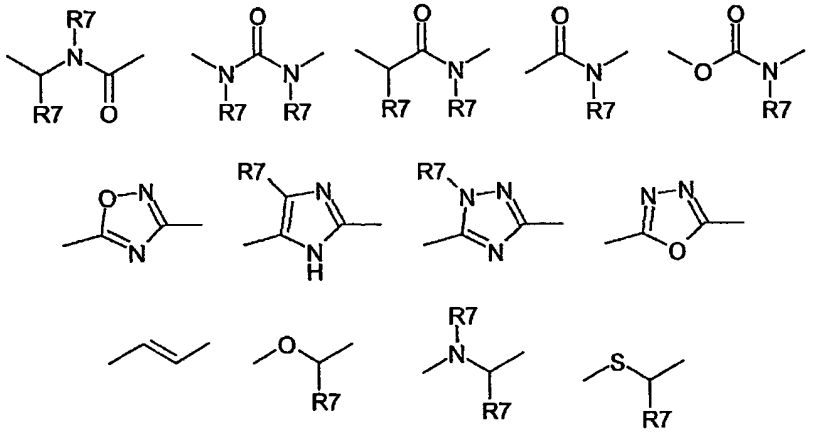


3. A compound according to claim 1 or 2, wherein R8 is



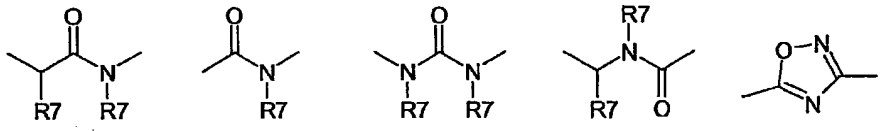
4. A compound according to claim 1 or 2, wherein R8 is selected from halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (*e.g.* $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -CF_3, -OCF_3, -SCF_3, SCH_3.

5. A compound according to any of the preceding claims wherein A is selected from the group consisting of:



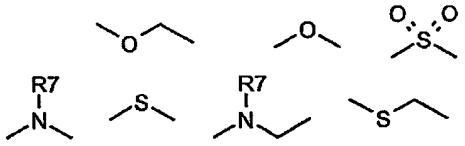
wherein R7 is as defined in claim 1.

6. A compound according to any of the preceding claims wherein A is selected from the group consisting of:



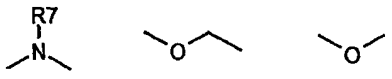
wherein R7 is as defined in claim 1.

7. A compound according to any claims 1-3, 5, 6, wherein B is a single bond or selected from the group consisting of:



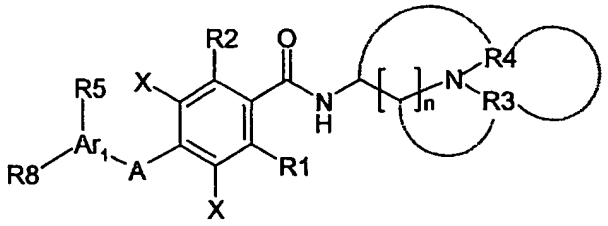
wherein R7 is as defined in claim 1.

8. A compound according to claim 7, wherein B is selected from the group consisting of:



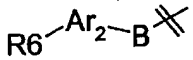
wherein R7 is as defined in claim 1.

9. A compound according to any of the preceding claims with the following structure



wherein Ar_1, Ar_2, A, B, R1, R2, R3, R4, R5, R6, R7, R8, X and n are defined as in claim 1.

10. A compound according to claim 9, wherein R8 is



11. A compound according to any of the preceding claims wherein the -B- moiety is not placed ortho to the -A- linker.

12. A compound according to any of the preceding claims, wherein Ar_1 and Ar_2 are the same or different aryl or heteroaryl groups such as, e.g., phenyl, pyridine, thiophene.

13. A compound according to any of the preceding claims, wherein R2 is hydrogen.

14. A compound according to any of the preceding claims, wherein R2 is hydrogen and X is H, F, Cl, Br, I, CF_3, OCF_3, SCF_3, SCH_3 or lower alkyl or alkenyl group.

15. A compound according to any of the preceding claims, wherein R2 is H and X is H or F.

16. A compound according to any of the preceding claims, wherein R5 and R6 may be the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkyamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, $CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

17. A compound according to any of the preceding claims in amorphous or crystalline form.

18. A compound according to any of the preceding claims in racemic or enantiomeric form.

19. A compound according to any of the preceding claims in the form of a physiologically acceptable salt, complex, solvate or prodrug thereof.

20. A compound according to any of the preceding claims for use in medicine.

21. A compound according to any of the preceding claims, which is an agent for preventing or treating diseases caused by or involving a melanin-concentrating hormone.

22. A compound according to any of the preceding claims, which modulates the activity of an MCH receptor.

23. A compound according to any of the preceding claims, which has antagonistic activity against an MCH receptor.

24. A compound according to any of claims 1-22, which has agonistic, inverse agonistic or allosteric activity against an MCH receptor.

25. A compound according to any of the preceding claims, wherein the MCH receptor has at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequence CTLITAMDAN or CTIITSLDTC

26. A compound according to any of the preceding claims, wherein the MCH receptor comprises the amino acid sequence CTLITAMDAN or CTIITSLDTC.

27. A compound according to any of the preceding claims, wherein the MCH receptor is an MCH1 or MCH2 receptor.

28. A compound according to any of the preceding claims, wherein the MCH receptor is an MCH1 receptor.

29. A compound according to any of the preceding claims, wherein the MCH receptor is a mammalian such as human receptor.

30. A compound according to any of the preceding claims, which is an agent for preventing or treating feeding disorders.

31. A compound according to any of claims 1-23 or 25-30, which is an agent for reducing body mass.

32. A compound according to any of claims 1-23 or 25-31, which is an agent for preventing or treating Syndrome X (metabolic syndrome), or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension.

33. A compound according to any of claims 1-23 or 25-31, which is an agent for preventing or treating Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM).

34. A compound according to any of claims 1-23 or 25-33, which is an agent for preventing or treating bulimia, obesity and/or bulimina nervosa.

35. A compound according to any of claims 1-29, which is an antidepressant and/or anti-anxiety agent.

36. A cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to any of claims 1-23 or 25-34.

37. A method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-35.

38. A method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-34.

39. A method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-34.

40. A method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-23 or 25-34.

41. A method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-23 or 25-34.

42. A method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-23 or 25-34.

43. A method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-23 or 25-34.

44. A method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-24 or 35.

45. A pharmaceutical composition comprising a compound according to any of the claims 1-35 or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

46. A pharmaceutical composition according to claim 45, wherein the compound is present in the form of a physiologically acceptable salt such as a salt formed between the compound and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_5 salt, or a salt formed between the compound and an organic acid such as organic acids like e.g. H_2CO_3, acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, C4H8(COOH)2, $C_5H_{10}(COOH)_2$, fumaric acid,

maleic acid, lactic acid, citric acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

47. A pharmaceutical composition according to claim 45 or 46 for enteral and/or parenteral use.

48. A pharmaceutical composition according to claim 45 or 46 for oral, buccal, rectal, nasal, topical, vaginal or ocular use.

49. A pharmaceutical composition according to any of claims 45-48 in the form of a solid, semi-solid or fluid composition.

50. A pharmaceutical composition according to claim 49 in solid form, wherein the composition is in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, or particulate material.

51. A pharmaceutical composition according to claim 49 in semi-solid form, wherein the composition is in the form of a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

52. A pharmaceutical composition according to claim 49 in fluid form, wherein the composition is in the form of a solution, an emulsion, a suspension, a dispersion, a liposomal composition, a spray, a mixture, or a syrup.

53. A pharmaceutical composition according to any of claims 46-52 comprising a therapeutically effective amount of a compound according to claims.

54. A pharmaceutical composition according to claim 53, wherein the amount is from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

55. Use of a compound according to any of claims 1-23 or 25-34 or a pharmaceutically acceptable salt thereof for the manufacture of a cosmetic composition for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto.

56. Use of a compound according to any of claims 1-35 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for i) the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, ii) the treatment and/or prophylaxis of diseases caused by feeding disorders, iii) modifying the feeding behaviour of a mammal, iv) the reduction of body mass, v) the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, or vi) the treatment and/or prophylaxis of depression and/or anxiety.

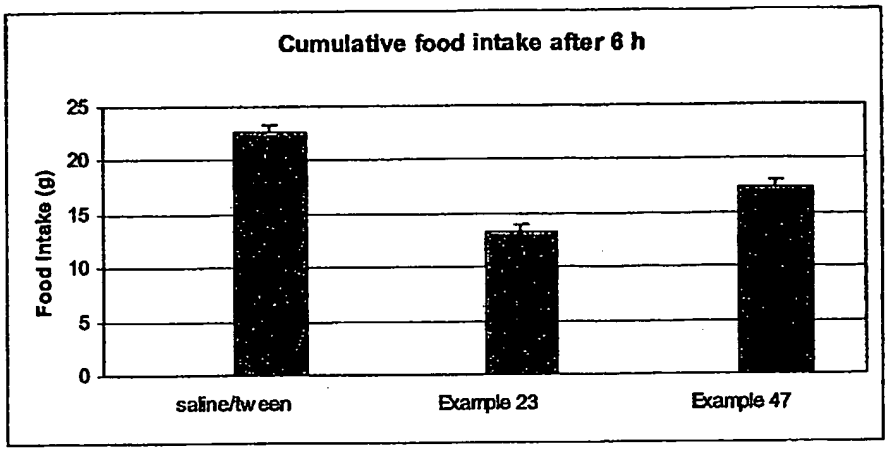

Cumulative food intake after 6 h
Food Intake (g)
25
20
15
10
5
0
saline/tween
Example 23
Example 47

Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00231

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/28 C07C237/34 A61K31/167 A61K31/17 A61P3/04
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 070494 A (ICOS CORP) 12 September 2002 (2002-09-12) claim ---	1-56
X	US 4 146 637 A (METZ GUNTER ET AL) 27 March 1979 (1979-03-27) table 1 example 17 ---	1,2,4-6, 9,12-20, 45-54
X	WO 01 21577 A (ISHIHARA YUJI ;KATO KANEYOSHI (JP); MORI MASAAKI (JP); SHIMOMURA Y) 29 March 2001 (2001-03-29) page 102 -page 103 -----	1-56

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	04 07 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GÖMEZ LAGERLÖF /EÖ

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interl ial application No.
PCT/DK 03/00231

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 37-44
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1-16
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 37-44

Claims 37-44 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1. (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Continuation of Box I.2

Claims Nos.: 1-16

Present claims 1-16 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds showed in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

on on patent family members

International Application No
PCT/DK 03/00231

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